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NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	AUG 10	Time limit for inactive STN sessions doubles to 40 minutes
NEWS 3	AUG 18	COMPENDEX indexing changed for the Corporate Source (CS) field
NEWS 4	AUG 24	ENCOMPLIT/ENCOMPLIT2 reloaded and enhanced
NEWS 5	AUG 24	CA/CAplus enhanced with legal status information for U.S. patents
NEWS 6	SEP 09	50 Millionth Unique Chemical Substance Recorded in CAS REGISTRY
NEWS 7	SEP 11	WPIDS, WPINDEX, and WPIX now include Japanese FTERM thesaurus
NEWS 8	OCT 21	Derwent World Patents Index Coverage of Indian and Taiwanese Content Expanded
NEWS 9	OCT 21	Derwent World Patents Index enhanced with human translated claims for Chinese Applications and Utility Models
NEWS 10	NOV 23	Addition of SCAN format to selected STN databases
NEWS 11	NOV 23	Annual Reload of IFI Databases
NEWS 12	DEC 01	FRFULL Content and Search Enhancements
NEWS 13	DEC 01	DGENE, USGENE, and PCTGEN: new percent identity feature for sorting BLAST answer sets
NEWS 14	DEC 02	Derwent World Patent Index: Japanese FI-TERM thesaurus added
NEWS 15	DEC 02	PCTGEN enhanced with patent family and legal status display data from INPADOCDB
NEWS 16	DEC 02	USGENE: Enhanced coverage of bibliographic and sequence information
NEWS 17	DEC 21	New Indicator Identifies Multiple Basic Patent Records Containing Equivalent Chemical Indexing in CA/CAplus
NEWS 18	JAN 12	Match STN Content and Features to Your Information Needs, Quickly and Conveniently
NEWS 19	JAN 25	Annual Reload of MEDLINE database

NEWS EXPRESS MAY 26 09 CURRENT WINDOWS VERSION IS V8.4,
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http://www.cas.org/support/stngen/stndoc/properties.html

=> s tetrahydrofolate
L1        3075 TETRAHYDROFOLATE

=> s tetrahydrofolate/cn
L2           0 TETRAHYDROFOLATE/CN

=> E "TETRAHYDROFOLATE"/CN 25
E1           1     TETRAHYDROFLUORAPHIN PERACETATE/CN
E2           1     TETRAHYDROFLUORENONE/CN
E3           0 --> TETRAHYDROFOLATE/CN
E4           1     TETRAHYDROFOLATE (PTERIDINE) DEHYDROGENASE/CN
E5           1     TETRAHYDROFOLATE DEHYDROGENASE/CN
E6           1     TETRAHYDROFOLATE DEHYDROGENASE (ESCHERICHIA COLI CLONE PLK0631
GENE DFR1 N-TERMINAL FRAGMENT)/CN
E7           1     TETRAHYDROFOLATE DEHYDROGENASE (ESCHERICHIA COLI STRAIN VA292
CLONE PDG0301 GENE DFRA7 TYPE VII)/CN
E8           1     TETRAHYDROFOLATE DEHYDROGENASE (ESCHERICHIA COLI)/CN
E9           1     TETRAHYDROFOLATE DEHYDROGENASE (XANTHOBACTER AUTOTROPHICUS GENE
MTDA)/CN
E10          1     TETRAHYDROFOLATE DEHYDROGENASE-LIKE PROTEIN 14 (HUMAN CLONE
PBS-0046D10)/CN
E11          1     TETRAHYDROFOLATE DEHYDROGENASE-THYMIDYLATE SYNTHASE (TETRAHYMENA
THERMOPHILA)/CN
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E12          1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (1.5.1.5)
(LACTOCOCCUS LACTIS LACTIS STRAIN IL1403 GENE FOLD)/CN
E13          1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (ARTHROBACTER
AURESCENS STRAIN TC1)/CN
E14          1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (BRUCELLA
MELITENSIS BIOVAR ABORTUS STRAIN 2308 GENE FOLD)/CN
E15          1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (NITROBACTER
WINOGRADSKYI STRAIN NB-255)/CN
E16          1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (NITROSOMONAS
EUROPAEA STRAIN ATCC 19718 GENE FOLD)/CN
E17          1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (PSYCHROBACTER
ARCTICUS STRAIN 273-4 GENE FOLD)/CN
E18          1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (STREPTOCOCCUS
MUTANS STRAIN UA159 GENE FOLD)/CN
E19          1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE, FOLD (CLOSTRIDIUM
ACETOBUTYLICUM STRAIN ATCC 824 GENE CAC2083)/CN
E20          1     TETRAHYDROFOLATE FORMYLASE/CN
E21          1     TETRAHYDROFOLATE METHYLTRANSFERASE/CN
E22          1     TETRAHYDROFOLATE REDUCTASE (HUMAN HERPESVIRUS 8)/CN
E23          1     TETRAHYDROFOLATE SYNTHASE/CN
E24          1     TETRAHYDROFOLATE SYNTHASE (YAMADAZYMA STIPITE STRAIN CBS 6054
GENE ADE3)/CN
E25          1     TETRAHYDROFOLATE SYNTHETASE/CN

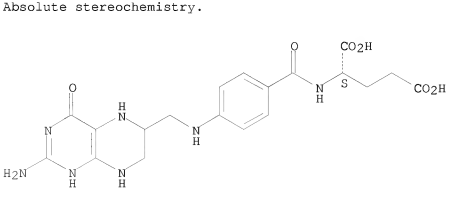
=> E "TETRAHYDROFOLIC ACID"/CN 25
E1           1     TETRAHYDROFOLATE-DEPENDENT 5-URACIL-TRNA TRANSFERASE/CN
E2           1     TETRAHYDROFOLATEQACEDELTA1 (SALMONELLA ENTERICA SUBSP. ENTERICA
STRAIN SRC19 GENE QACEDELTA1)/CN
E3           1 --> TETRAHYDROFOLIC ACID/CN
E4           1     TETRAHYDROFOLIC ACID DIAMIDE/CN
E5           1     TETRAHYDROFOLIC ACID DIHYDROCHLORIDE/CN
E6           1     TETRAHYDROFOLIC FORMYLASE/CN
E7           1     TETRAHYDROFOLIMININE/CN
E8           1     TETRAHYDROFOLIMININE, TETRAHYDRO-/CN
E9           1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE (CRYPTOCOCCUS NEOFORMANS
NEOFORMANS STRAIN JEC21)/CN
E10          1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE (FOLYLPOLYGLUTAMATE
SYNTHETASE) (CYTOPHAGA HUTCHINSONII STRAIN ATCC 33406 GENE FOLC)/CN
E11          1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE (FRANCISELLA TULARENSIS
HOLARCTICA STRAIN OSU18)/CN
E12          1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE (RHODOCOCCUS STRAIN
RHA1)/CN
E13          1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE PRECURSOR (ARABIDOPSIS
THALIANA CLONE RAFL07-10-D06 (R10837) GENE AT3G55630)/CN
E14          1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE-RELATED PROTEIN
(THERMOPLASMA ACIDOPHILUM STRAIN DSM1728 GENE TA0637)/CN
E15          1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE/DIHYDROFOLATE SYNTHASE
(MYXOCOCCUS XANTHUS STRAIN DK 1622 GENE FOLC)/CN
E16          1     TETRAHYDROFREDERICAMYCIN/CN
E17          1     TETRAHYDROFUGAPAVINE/CN
E18          1     TETRAHYDROFUGAPAVINE OXIME/CN
E19          1     TETRAHYDROFUGAPAVINE OXIME OXALATE/CN
E20          1     TETRAHYDROFULLERENE-C60/CN
E21          1     TETRAHYDROFUMITREMORGIN B/CN
E22          1     TETRAHYDROFUNICULOSIN/CN
E23          1     TETRAHYDROFURAN/CN
E24          1     TETRAHYDROFURAN COMPD. WITH CHLORINE (1:1)/CN
E25          1     TETRAHYDROFURAN COMPD. WITH HYDROGEN CHLORIDE (1:1)/CN

=> S E3
L3           1 "TETRAHYDROFOLIC ACID"/CN
```

=> DIS L3 1 SQIDE

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2010 ACS on STN
RN 135-16-0 REGISTRY
CN L-Glutamic acid, N-[4-[[(2-amino-3,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glutamic acid, N-[p-[[(2-amino-3,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-, L- (7CI, 8CI)
CN L-Glutamic acid, N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI)
OTHER NAMES:
CN (-)-L-5,6,7,8-Tetrahydrofolic acid
CN 5,6,7,8-Tetrahydrofolic acid
CN L-5,6,7,8-Tetrahydrofolic acid
CN Tetrahydrofolic acid
CN Tetrahydropteroylglutamic acid
CN THFA
FS STEREOSEARCH
DR 60201-89-0, 18632-03-6, 14231-42-6, 15582-27-1, 4172-42-3
MF C19 H23 N7 O6
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IPA, MSDS-OHS, PIRA, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL, USPATOLD, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.



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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

            1251 REFERENCES IN FILE CA (1907 TO DATE)
              95 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            1253 REFERENCES IN FILE CAPLUS (1907 TO DATE)


=> E "TETRAHYDROFOLIC ACID"/CN 25
E1            1     TETRAHYDROFOLATE-DEPENDENT 5-URACIL-TRNA TRANSFERASE/CN
E2            1     TETRAHYDROFOLATEQACEDELTA1 (SALMONELLA ENTERICA SUBSP. ENTERICA
STRAIN SRC19 GENE QACEDELTA1)/CN
E3            1 --> TETRAHYDROFOLIC ACID/CN
E4            1     TETRAHYDROFOLIC ACID DIAMIDE/CN
E5            1     TETRAHYDROFOLIC ACID DIHYDROCHLORIDE/CN
E6            1     TETRAHYDROFOLIC FORMYLASE/CN
E7            1     TETRAHYDROFOLIMININE/CN
E8            1     TETRAHYDROFOLIMININE, TETRAHYDRO-/CN
E9            1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE (CRYPTOCOCCUS NEOFORMANS
NEOFORMANS STRAIN JEC21)/CN
E10           1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE (FOLYLPOLYGLUTAMATE
SYNTHETASE) (CYTOPHAGA HUTCHINSONII STRAIN ATCC 33406 GENE FOLC)/CN
E11           1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE (FRANCISELLA TULARENSIS
HOLARCTICA STRAIN OSU18)/CN
E12           1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE (RHODOCOCCUS STRAIN
RHA1)/CN
E13           1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE PRECURSOR (ARABIDOPSIS
THALIANA CLONE RAFL07-10-D06 (R10837) GENE AT3G55630)/CN
E14           1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE-RELATED PROTEIN
(THERMOPLASMA ACIDOPHILUM STRAIN DSM1728 GENE TA0637)/CN
E15           1     TETRAHYDROFOLYLPOLYGLUTAMATE SYNTHASE/DIHYDROFOLATE SYNTHASE
(MYXOCOCCUS XANTHUS STRAIN DK 1622 GENE FOLC)/CN
E16           1     TETRAHYDROFREDERICAMYCIN/CN
E17           1     TETRAHYDROFUGAPAVINE/CN
E18           1     TETRAHYDROFUGAPAVINE OXIME/CN
E19           1     TETRAHYDROFUGAPAVINE OXIME OXALATE/CN
E20           1     TETRAHYDROFULLERENE-C60/CN
E21           1     TETRAHYDROFUMITREMORGIN B/CN
E22           1     TETRAHYDROFUNICULOSIN/CN
E23           1     TETRAHYDROFURAN/CN
E24           1     TETRAHYDROFURAN COMPD. WITH CHLORINE (1:1)/CN
E25           1     TETRAHYDROFURAN COMPD. WITH HYDROGEN CHLORIDE (1:1)/CN

=> E "METHYL-TETRAHYDROFOLATE"/CN 25
E1            1     METHYL-TERT-BUTYLVINYLETHYNYLCARBINOL/CN
E2            1     METHYL-TERT-PENTYLCARBINOL/CN
E3            0 --> METHYL-TETRAHYDROFOLATE/CN
E4            1     METHYL-TRANS,TRAN-6-OXO-2,4-HEPTADIENOATE/CN
E5            1     METHYL-TRANS-B-CHLOROACRYLATE/CN
E6            1     METHYL-TRANS-11-HYDROPEROXY-9-UNDECENOATE/CN
E7            1     METHYL-TRANS-P-(METHYLCARBAMOYLOXY)CINNAMATE/CN
E8            1     METHYL-TRANSFERASE (SINORHIZOBIUM MELILOTI GENE SMB21433)/CN
E9            1     METHYL-TRANSFERASE (THIOBACILLUS DENITRIFICANS STRAIN ATCC
25259)/CN
E10           1     METHYL-TRI-N-OCTYLAMMONIUM NITRATE/CN
E11           1     METHYL-TRI-TETRADECYLPHOSPHONIUM TETRAFLUOROBORATE/CN
E12           1     METHYL-VIOLOGEN-REDUCING HYDROGENASE, DELTA SUBUNIT
(DESULFOTALEA PSYCHROPHILA STRAIN LSV54)/CN
E13           4     METHYL-VIOLOGEN-REDUCING HYDROGENASE, DELTA SUBUNIT (SYNTROPHUS
ACIDITROPHICUS STRAIN SB)/CN
E14           1     METHYL/ACCEPTING CHEMOTAXIS PROTEIN. (RHIZOBIUM ETLI STRAIN
CFN42 PLASMID P42D GENE MCPG)/CN
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E15          1     METHYLACCA/CN
E16          1     METHYLACENAPHTHENE/CN
E17          1     METHYLACENAPHTHYLENE/CN
E18          1     METHYLACETALDEHYDE/CN
E19          1     METHYLACETAMIDE/CN
E20          1     METHYLACETAZOLAMIDE/CN
E21          1     METHYLACETHION/CN
E22          1     METHYLACETIC ACID/CN
E23          1     METHYLACETIC ANHYDRIDE/CN
E24          1     METHYLACETOIN/CN
E25          1     METHYLACETONOCHLOROPHOS-3/CN

=> E "5-METHYLTETRAHYDROFOLATE"/CN 25
E1           1     5-METHYLTETRAHYDRO-2-FURALDEHYDE/CN
E2           1     5-METHYLTETRAHYDRO-2-FURANONE/CN
E3           0 --> 5-METHYLTETRAHYDROFOLATE/CN
E4           1     5-METHYLTETRAHYDROFOLATE --HOMOCYSTEINE METHYLTRANSFERASE
(BRUCELLA MELITENSIS BIOVAR SUIS STRAIN 1330 GENE METH)/CN
E5           1     5-METHYLTETRAHYDROFOLATE --HOMOCYSTEINE METHYLTRANSFERASE
(BRUCELLA MELITENSIS STRAIN 16M GENE BMEI1759)/CN
E6           1     5-METHYLTETRAHYDROFOLATE --HOMOCYSTEINE METHYLTRANSFERASE
(FUSOBACTERIUM NUCLEATUM NUCLEATUM STRAIN ATCC25586 GENE FN0163)/CN
E7           1     5-METHYLTETRAHYDROFOLATE --HOMOCYSTEINE METHYLTRANSFERASE
(STREPTOCOCCUS AGALACTIAE STRAIN 2603V/R GENE SAG2048)/CN
E8           1     5-METHYLTETRAHYDROFOLATE --HOMOCYSTEINE METHYLTRANSFERASE
(THERMOSYNECHOCOCCUS ELONGATUS STRAIN BP-1 GENE METH)/CN
E9           1     5-METHYLTETRAHYDROFOLATE --HOMOCYSTEINE S-METHYLTRANSFERASE
(NOSTOC SP. PCC 7120 GENE ALR0308)/CN
E10          1     5-METHYLTETRAHYDROFOLATE -HOMOCYSTEINE METHYL TRANSFERASE
(XANTHOMONAS AXONOPODIS CITRI STRAIN 306 GENE METH)/CN
E11          1     5-METHYLTETRAHYDROFOLATE -HOMOCYSTEINE METHYL TRANSFERASE
(XANTHOMONAS CAMPESTRIS CAMPESTRIS STRAIN ATCC33913 GENE METH1)/CN
E12          1     5-METHYLTETRAHYDROFOLATE -HOMOCYSTEINE METHYLTRANSFERASE
(CHLOROBIUM TEPIDUM STRAIN TLS GENE METH)/CN
E13          1     5-METHYLTETRAHYDROFOLATE -HOMOCYSTEINE METHYLTRANSFERASE
(MYCOBACTERIUM TUBERCULOSIS STRAIN CDC1551 GENE MT2183)/CN
E14          1     5-METHYLTETRAHYDROFOLATE -HOMOCYSTEINE METHYLTRANSFERASE
(XANTHOMONAS AXONOPODIS CITRI STRAIN 306 GENE METH)/CN
E15          1     5-METHYLTETRAHYDROFOLATE -HOMOCYSTEINE METHYLTRANSFERASE
(XANTHOMONAS CAMPESTRIS CAMPESTRIS STRAIN ATCC33913 GENE METH2)/CN
E16          1     5-METHYLTETRAHYDROFOLATE CORRINOID/IRON SULFUR PROTEIN
METHYLTRANSFERASE (CARBOXYDOTHERMUS HYDROGENOFORMANS STRAIN Z-2901 GENE ACSE)/CN
E17          1     5-METHYLTETRAHYDROFOLATE S-HOMOCYSTEINE METHYLTRANSFERASE
(GEOBACILLUS THERMODENITRIFICANS STRAIN NG80-2 GENE METH)/CN
E18          1     5-METHYLTETRAHYDROFOLATE S-HOMOCYSTEINE METHYLTRANSFERASE
(MESORHIZOBIUM LOTI STRAIN MAFF303099 GENE MLR1220)/CN
E19          1     5-METHYLTETRAHYDROFOLATE S-HOMOCYSTEINE METHYLTRANSFERASE
(MESORHIZOBIUM LOTI STRAIN MAFF303099 GENE MLR1243)/CN
E20          1     5-METHYLTETRAHYDROFOLATE S-HOMOCYSTEINE METHYLTRANSFERASE
(SYMBIOBACTERIUM THERMOPHILUM STRAIN IAM14863)/CN
E21          1     5-METHYLTETRAHYDROFOLATE S-HOMOCYSTEINE METHYLTRANSFERASE
(THERMOTOGA MARITIMA GENE TM0268)/CN
E22          1     5-METHYLTETRAHYDROFOLATE TRIGLUTAMATE/CN
E23          1     5-METHYLTETRAHYDROFOLATE--HOMOCYSTEIN METHYLTRANSFERASE METH
(METHIONINE SYNTHASE, VITAMIN-B12 DEPENDENT ISOZYME) (MS) (MYCOBACTERIUM BCG STRAIN
PASTEUR 1173P2 GENE METH)/CN
E24          1     5-METHYLTETRAHYDROFOLATE--HOMOCYSTEINE METHYLTRANSFERASE
(ALCANIVORAX BORKUMENSIS STRAIN SK2)/CN
E25          1     5-METHYLTETRAHYDROFOLATE--HOMOCYSTEINE METHYLTRANSFERASE
(BACILLUS ANTHRACIS STRAIN AMES ANCESTOR A2084 GENE METH)/CN

=> E "5-MTHF"/CN 25
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E1            1      5-MOT/CN
E2            1      5-MTH PTEROYLTRIGLUTAMATE--HOMOCYSTEINE METHYLTRANSFERASE
(YERSINIA PSEUDOTUBERCULOSIS STRAIN IP32953 GENE METE)/CN
E3            0 --> 5-MTHF/CN
E4            1      5-N,N-BIS(2-CHLOROETHYL)AMINOURACIL/CN
E5            1      5-N,N-BIS(CARBOXYMETHYL)AMINOMETHYLVANILLIN/CN
E6            1      5-N,N-DIETHYLALANYL-5-METHYL-5H-DIBENZ(B,F)AZEPINIUM IODIDE/CN
E7            1
5-N,N-DIETHYLAMINO-7-PROPYL-6-((2'-(1H-TETRAZOL-5-YL)BIPHENYL-4-YL)METHYL)-1,2,4-TRI
AZOLO(1,5-A)PYRIMIDINE/CN
E8            1      5-N,N-DIETHYLAMINOCARBONYLBICYCLO(2.2.1)-2-HEPTENE/CN
E9            1      5-N,N-DIISOPROPYLAMINO-1-PENTENE-1-HEXENE COPOLYMER/CN
E10           1      5-N,N-DIMETHYL-B-ALANYLURACIL HYDROCHLORIDE/CN
E11           1      5-N,N-DIMETHYLAMILORIDE/CN
E12           1      5-N,N-DIMETHYLAMINO-2,1,3-BENZOXADIAZOLE/CN
E13           1      5-N,N-DIMETHYLAMINO-2-HYDROXYBENZALDOXIME/CN
E14           1      5-N,N-DIMETHYLAMINO-3-PENTYNYL DIPHENYLPHOSPHINITE/CN
E15           1      5-N,N-DIMETHYLAMINO-3-PENTYNYLDIPHENYLPHOSPHINE/CN
E16           1
5-N,N-METHYLACRYLAMIDO-5-HYDROXYMETHYL-2,2-DIMETHYL-1,3-DIOXANE/CN
E17           1      5-N-((R)-3,7-DIMETHYLOCTYLAMINO)CARBONYL ISOPHTHALIC ACID/CN
E18           1      5-N-((R)-3,7-DIMETHYLOCTYLAMINO)CARBONYL ISOPHTHALOYL CHLORIDE/CN
E19           1      5-N-(B-HYDROXYETHYL)AMINO-2-METHYLPHENOL/CN
E20           1      5-N-(B-HYDROXYETHYL)AMINO-4-METHOXY-2-METHYLPHENOL/CN
E21           1
5-N-(2-(2-METHOXYETHOXY)ETHYLIMINO)-2,2,6,6-TETRAMETHYL-3-HEPTANONE/CN
E22           1      5-N-(2-HYDROXY)HENEICOSYLRESORCINOL/CN
E23           1      5-N-(2-HYDROXY)TRICOSYLRESORCINOL/CN
E24           1      5-N-(2-METHOXYETHYLIMINO)-2,2,6,6-TETRAMETHYL-3-HEPTANONE/CN
E25           1      5-N-(OCTADECANOYL)AMINOFLUORESCEIN/CN

=> E "5,10-METHYLENETETRA"/CN 25
E1            1      5,10-METHYLENE-TETRAHYDROFOLATE REDUCTASE (SHIGELLA FLEXNERI
STRAIN 2457T GENE METF)/CN
E2            1      5,10-METHYLENE-TETRAHYDROFOLATE REDUCTASE (STREPTOMYCES
CINNAMONENSIS STRAIN DSM-1042 GENE FNQ15 SEQUENCE HOMOLOG)/CN
E3            0 --> 5,10-METHYLENETETRA/CN
E4            1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (AGROBACTERIUM
TUMEFACIENS STRAIN C58 GENE METF)/CN
E5            1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (BRUCELLA MELITENSIS
BIOVAR SUIS STRAIN 1330 GENE METF)/CN
E6            1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (BRUCELLA MELITENSIS
STRAIN 16M GENE BMEI0559)/CN
E7            1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (BUCHNERA APHIDICOLA
STRAIN SG GENE METF)/CN
E8            1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (CHLOROBIUM TEPIDUM
STRAIN TLS GENE METF)/CN
E9            1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (FADH) (METHANOSARCINA
ACETIVORANS STRAIN C2A GENE METF)/CN
E10           1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (MESORHIZOBIUM LOTI
STRAIN MAFF303099 GENE MLL1587)/CN
E11           1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (SALMONELLA ENTERICA
TYPHIMURIUM STRAIN LT2; SGSC 1412; ATCC 700720 GENE METF)/CN
E12           1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (SHIGELLA FLEXNERI
STRAIN 301 GENE METF)/CN
E13           1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (STREPTOCOCCUS
PNEUMONIAE STRAIN TIGR4 GENE SP0586)/CN
E14           1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (STREPTOMYCES
COELICOLOR STRAIN A3(2) GENE SC4A10.36C)/CN
E15           1      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (THERMOANAEROBACTER
TENGCONGENSIS STRAIN MB4T GENE METF)/CN
E16           2      5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (XANTHOMONAS
AXONOPODIS CITRI STRAIN 306 GENE METF)/CN
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E17          2     5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (XANTHOMONAS
CAMPESTRIS CAMPESTRIS STRAIN ATCC33913 GENE METF)/CN
E18          1     5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (YERSINIA PESTIS
STRAIN KIM GENE METF)/CN
E19          1     5,10-METHYLENETETRAHYDROFOLATE DEHYDROGENASE/CN
E20          1     5,10-METHYLENETETRAHYDROFOLATE DEHYDROGENASE (LEGIONELLA
PNEUMOPHILA PNEUMOPHILA STRAIN PHILADELPHIA 1 GENE FOLD)/CN
E21          2     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE/CN
E22          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (ACINETOBACTER STRAIN
ADP1 GENE METF)/CN
E23          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (AEROMONAS HYDROPHILA
HYDROPHILA STRAIN ATCC 7966 GENE METF)/CN
E24          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (ALCANIVORAX
BORKUMENSIS STRAIN SK2 GENE METF)/CN
E25          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (AQUIFEX AEOLICUS GENE
METF)/CN

=> E "5,10-METHYLENETETRAHYDROFOLATE"/CN 25
E1           2     5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (XANTHOMONAS
CAMPESTRIS CAMPESTRIS STRAIN ATCC33913 GENE METF)/CN
E2           1     5,10-METHYLENETETRAHYDRO FOLATE REDUCTASE (YERSINIA PESTIS
STRAIN KIM GENE METF)/CN
E3           0 --> 5,10-METHYLENETETRAHYDROFOLATE/CN
E4           1     5,10-METHYLENETETRAHYDROFOLATE DEHYDROGENASE/CN
E5           1     5,10-METHYLENETETRAHYDROFOLATE DEHYDROGENASE (LEGIONELLA
PNEUMOPHILA PNEUMOPHILA STRAIN PHILADELPHIA 1 GENE FOLD)/CN
E6           2     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE/CN
E7           1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (ACINETOBACTER STRAIN
ADP1 GENE METF)/CN
E8           1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (AEROMONAS HYDROPHILA
HYDROPHILA STRAIN ATCC 7966 GENE METF)/CN
E9           1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (ALCANIVORAX
BORKUMENSIS STRAIN SK2 GENE METF)/CN
E10          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (AQUIFEX AEOLICUS GENE
METF)/CN
E11          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BACTEROIDES FRAGILIS
STRAIN ATCC25285)/CN
E12          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BACTEROIDES FRAGILIS
STRAIN YCH46)/CN
E13          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BACTEROIDES
THETAIOTAOMICRON STRAIN VPI-5482 GENE BT3821)/CN
E14          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BAUMANNIA
CICADELLINICOLA STRAIN HC (HOMALODISCA COAGULATA) GENE METF)/CN
E15          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BIFIDOBACTERIUM LONGUM
STRAIN NCC2705 GENE METF)/CN
E16          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BLATTABACTERIUM SP.
(PERIPLANETA AMERICANA) STR. BPLAN STRAIN BPLAN GENE METF)/CN
E17          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BORDETELLA AVIUM
STRAIN 197N GENE METF)/CN
E18          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BRADYRHIZOBIUM
JAPONICUM STRAIN USDA110 GENE METF)/CN
E19          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BRADYRHIZOBIUM STRAIN
BTAI1 GENE METF)/CN
E20          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BRADYRHIZOBIUM STRAIN
ORS278 GENE METF)/CN
E21          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BUCHNERA APHICICOLA
STRAIN BAIZONGIA PISTACIAE GENE METF)/CN
E22          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BUCHNERA APHIDICOLA
STRAIN CC GENE METF)/CN
E23          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BUCHNERA STRAIN APS
GENE METF)/CN
E24          1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BURKHOLDERIA MALLEI
STRAIN ATCC 23344 GENE METF)/CN
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E25           1     5,10-METHYLENETETRAHYDROFOLATE REDUCTASE (BURKHOLDERIA
PSEUDOMALLEI STRAIN K96243 GENE METF)/CN

=> E "MTHF"/CN 25
E1            1     MTHANAMINE, N-(2-NAPHTHALENYLMETHYLENE)-, N-OXIDE, (N(E))-/CN
E2            1     MTHANIMINE, N-((5-NITRO-2-FURANYL)METHYLENE)-, N-OXIDE,
(N(Z))-/CN
E3            1 --> MTHF/CN
E4            1     MTHFD1 PROTEIN (HUMAN CLONE IMAGE:3344724 GENE MTHFD1)/CN
E5            1     MTHFD1 PROTEIN (XENOPUS TROPICALIS CLONE MGC:79474 IMAGE:6976340
GENE MTHFD1)/CN
E6            1     MTHFD1-PROV PROTEIN (XENOPUS LAEVIS CLONE MGC:53151
IMAGE:5542750)/CN
E7            1     MTHFD2 PROTEIN (HUMAN CLONE MGC:13506 IMAGE:4285669)/CN
E8            1     MTHFD2-PROV PROTEIN (XENOPUS LAEVIS CLONE MGC:82516
IMAGE:4963665 GENE MTHFD2-PROV)/CN
E9            1     MTHFR PROTEIN (HUMAN CLONE IMAGE:4299889)/CN
E10           1     MTHFR PROTEIN (MOUSE CLONE MGC:54647 IMAGE:6308248)/CN
E11           1     MTHFR-PROV PROTEIN (XENOPUS LAEVIS CLONE MGC:53253
IMAGE:5543666)/CN
E12           1     MTHFS PROTEIN (HUMAN CLONE IMAGE:3858004 GENE MTHFS)/CN
E13           1     MTHFS PROTEIN (MOUSE STRAIN MIX FVB/N, C57BL/6J CLONE MGC:37660
IMAGE:5026828)/CN
E14           1     MTHK-LIKE CALCIUM-GATED POTASSIUM CHANNEL (GRAMELLA FORSETII
STRAIN KT0803)/CN
E15           1     MTHPBC/CN
E16           1     MTHPC/CN
E17           1     MTHSP75 (HUMAN CELL LINE HELA GENE MTHSP75)/CN
E18           2     MTI/CN
E19           1     MTI 334/CN
E20           1     MTI 446/CN
E21           1     MTI 500/CN
E22           1     MTI 501/CN
E23           1     MTI 732/CN
E24           1     MTI 790/CN
E25           1     MTI 800/CN

=> S E3
L4            1 MTHF/CN

=> DIS L4 1 SQIDE

L4   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2010 ACS on STN
RN   96-47-9  REGISTRY
CN   Furan, tetrahydro-2-methyl-  (CA INDEX NAME)
OTHER NAMES:
CN   (±)-2-Methyltetrahydrofuran
CN   2-Methyltetrahydrofuran
CN   MTHF
CN   NSC 2115
CN   Tetrahydro-2-methylfuran
CN   Tetrahydrosylvan
DR   74069-67-3
MF   C5 H10 O
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, CA,
       CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN,
       CSCHEM, CSNB, DETHERM*, GMELIN*, IFICDB, IFIPAT, IFIUDB, MRCK*,
       MSDS-OHS, NAPRALERT, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, USPAT2,
       USPATFULL, USPATOLD
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**, NDSL**, TSCA**
```

(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Preprint; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); PRPH (Prophetic); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1868 REFERENCES IN FILE CA (1907 TO DATE)
18 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1875 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d his

(FILE 'HOME' ENTERED AT 13:07:18 ON 29 JAN 2010)

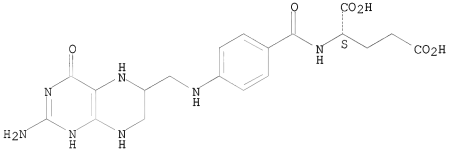
FILE 'REGISTRY' ENTERED AT 13:08:22 ON 29 JAN 2010
L1 3075 S TETRAHYDROFOLATE
L2 0 S TETRAHYDROFOLATE/CN
E "TETRAHYDROFOLATE"/CN 25
E "TETRAHYDROFOLIC ACID"/CN 25
L3 1 S E3
E "TETRAHYDROFOLIC ACID"/CN 25
E "METHYL-TETRAHYDROFOLATE"/CN 25
E "5-METHYLTETRAHYDROFOLATE"/CN 25
E "5-MTHF"/CN 25
E "5,10-METHYLENETETRA"/CN 25
E "5,10-METHYLENETETRAHYDROFOLATE"/CN 25
E "MTHF"/CN 25
L4 1 S E3

=> d l3

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2010 ACS on STN
RN 135-16-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN L-Glutamic acid, N-[4-[[(2-amino-3,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glutamic acid, N-[p-[[(2-amino-3,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-, L- (7CI, 8CI)
CN L-Glutamic acid, N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-

pteridinyl)methyl]amino]benzoyl]- (9CI)
OTHER NAMES:
CN (-)-L-5,6,7,8-Tetrahydrofolic acid
CN 5,6,7,8-Tetrahydrofolic acid
CN L-5,6,7,8-Tetrahydrofolic acid
CN Tetrahydrofolic acid
CN Tetrahydropteroylglutamic acid
CN THFA
FS STEREOSEARCH
DR 60201-89-0, 18632-03-6, 14231-42-6, 15582-27-1, 4172-42-3
MF C19 H23 N7 O6
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IPA, MSDS-OHS, PIRA, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL, USPATOLD, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1251 REFERENCES IN FILE CA (1907 TO DATE)
95 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1253 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	32.22	32.66

FILE 'CAPLUS' ENTERED AT 13:13:16 ON 29 JAN 2010
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FILE COVERS 1907 - 29 Jan 2010 VOL 152 ISS 6
FILE LAST UPDATED: 28 Jan 2010 (20100128/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2009

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the third quarter of 2009.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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=> s l3 or methylene-tetrahydrofolate or methyl-tetrahydrofolate
          1253 L3
        143321 METHYLENE
           943 METHYLENES
        143881 METHYLENE
                  (METHYLENE OR METHYLENES)
          3401 TETRAHYDROFOLATE
            96 TETRAHYDROFOLATES
          3449 TETRAHYDROFOLATE
                  (TETRAHYDROFOLATE OR TETRAHYDROFOLATES)
           679 METHYLENE-TETRAHYDROFOLATE
                  (METHYLENE(W)TETRAHYDROFOLATE)
       1131430 METHYL
           764 METHYLS
       1131884 METHYL
                  (METHYL OR METHYLS)
          3401 TETRAHYDROFOLATE
            96 TETRAHYDROFOLATES
          3449 TETRAHYDROFOLATE
                  (TETRAHYDROFOLATE OR TETRAHYDROFOLATES)
            87 METHYL-TETRAHYDROFOLATE
                  (METHYL(W)TETRAHYDROFOLATE)
L5        1971 L3 OR METHYLENE-TETRAHYDROFOLATE OR METHYL-TETRAHYDROFOLATE

=> s l5 and (pemetrexed or ralitrexed or lometrexol)
           750 PEMETREXED
             4 RALITREXED
           102 LOMETREXOL
L6           8 L5 AND (PEMETREXED OR RALITREXED OR LOMETREXOL)

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7           8 DUP REM L6 (0 DUPLICATES REMOVED)

=> d l7 1-8 ibib abs

L7   ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER:         2008:472492  CAPLUS
DOCUMENT NUMBER:          148:485895
TITLE:                    Efficient synthesis of chelators for nuclear imaging
                          and radiotherapy: compositions and applications
INVENTOR(S):              Yang, David J.; Yu, Dongfang
PATENT ASSIGNEE(S):       The University of Texas System, USA
```

SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008045604	A2	20080417	WO 2007-US72669	20070702
WO 2008045604	A3	20090226		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
US 20080107598	A1	20080508	US 2007-770395	20070628
AU 2007308022	A1	20080417	AU 2007-308022	20070702
AU 2007308022	A2	20090730		
CA 2664826	A1	20080417	CA 2007-2664826	20070702
KR 2009077942	A	20090716	KR 2009-709291	20070702
EP 2079486	A2	20090722	EP 2007-799253	20070702
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
IN 2009DN02008	A	20090731	IN 2009-DN2008	20090325
NO 2009001379	A	20090421	NO 2009-1379	20090403

PRIORITY APPLN. INFO.: US 2006-828347P P 20061005
US 2007-770395 A 20070628
WO 2007-US72669 W 20070702

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 148:485895

AB Novel methods of synthesis of chelator-targeting ligand conjugates, compns. comprising such conjugates, and therapeutic and diagnostic applications of such conjugates are disclosed. The compns. include chelator-targeting ligand conjugates optionally chelated to one or more metal ions. Methods of synthesizing these compns. in high purity are also presented. Also disclosed are methods of imaging, treating and diagnosing disease in a subject using these novel compns., such as methods of imaging a tumor within a subject and methods of diagnosing myocardial ischemia. For example, the multistep method of preparation of 187ReOL and 99mTcOL (H2L = [HSCH2CH(R)NHCH2]2 (RH = D-glucosamine)) is described which involves the preparation of H2L from L-cysteine hydrochloride and H2CO followed by successive reactions with PhCH2Cl, benzyl orthoformate, tetraacetylated D-glucosamine hydrochloride and deprotection. 187ReOL and 99mTcOL were prepared from 187ReOCl3(PPh3)2 or 99mTcO4- and H2L.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L7 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2007:654988 CAPLUS
DOCUMENT NUMBER: 147:377847
TITLE: A Randomized, Double-Blind, Phase II Study of Two Doses of Pemetrexed as First-Line Chemotherapy for Advanced Breast Cancer

AUTHOR(S): Llombart-Cussac, Antonio; Martin, Miguel; Harbeck, Nadia; Anghel, Rodica M.; Eniu, Alexandra E.; Verrill, Mark W.; Neven, Patrick; De Greve, Jacques; Melemed, Allen S.; Clark, Romnee; Simms, Lorinda; Kaiser, Christopher J.; Ma, Doreen

CORPORATE SOURCE: Hospital Universitario Arnau Vilanova, Lleida, Spain

SOURCE: Clinical Cancer Research (2007), 13(12), 3652-3659 CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB PURPOSE: Pemetrexed has shown varied response rates in advanced breast cancer. This randomized, double-blind, phase II study was conducted to assess the efficacy and safety of two doses of pemetrexed in a homogeneous population. A secondary objective was to identify mol. biomarkers correlating with response and toxicity. Exptl. DESIGN: Patients with newly diagnosed metastatic breast cancer or locally recurrent breast cancer received 600 mg/m2 (P600 arm) or 900 mg/m2 (P900 arm) of pemetrexed on day 1 of a 21-day cycle. All patients received folic acid and vitamin B12 supplementation. RESULTS: The P600 (47 patients) and P900 (45 patients) arms had response rates of 17.0% (95% confidence interval, 7.7-30.8%) and 15.6% (95% confidence interval, 6.5-29.5%) with .apprx.50% stable disease per arm, median progression-free survival of 4.2 and 4.1 mo, and median times to tumor progression of 4.2 and 4.6 mo, resp. Both arms exhibited minimal toxicity (grade 3/4 neutropenia <20%, leukopenia <9%, and other toxicities <5%). Tumor samples from 49 patients were assessed for the expression levels of 12 pemetrexed-related genes. Folylpolyglutamate synthetase and thymidine phosphorylase correlated with efficacy. Best response rates and median time to tumor progression for high vs. low thymidine phosphorylase expression were 27.6% vs. 6.3% (P = 0.023) and 5.4 vs. 1.9 mo (P = 0.076), and for folylpolyglutamate synthetase were 37.5% vs. 10.0% (P = 0.115) and 8.6 vs. 3.0 mo (P = 0.019), resp. γ-Glutamyl hydrolase expression correlated with grade 3/4 toxicities: 78.6% for high vs. 27.3% for low γ-glutamyl hydrolase (P = 0.024). CONCLUSION: The two pemetrexed doses yielded similar efficacy and safety profiles. Exploratory biomarker anal. identified efficacy and toxicity correlations and warrants further evaluation.

OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2007:923137 CAPLUS

DOCUMENT NUMBER: 148:372896

TITLE: Dose-dependent effects of (anti)folate preinjection on 99mTc-radiofolate uptake in tumors and kidneys

AUTHOR(S): Mueller, Cristina; Schibli, Roger; Forrer, Flavio; Krenning, Eric P.; de Jong, Marion

CORPORATE SOURCE: Department of Nuclear Medicine, Erasmus MC, Rotterdam, 3015 CE, Neth.

SOURCE: Nuclear Medicine and Biology (2007), 34(6), 603-608 CODEN: NMBIEO; ISSN: 0969-8051

PUBLISHER: Elsevier Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Introduction: The folate receptor (FR) is frequently overexpressed in tumors and can be targeted with folate-based (radio)pharmaceuticals. However, significant accumulation of radiofolates in FR-pos. kidneys represents a drawback. We have shown that preadministration of the antifolate pemetrexed (PMX) significantly improved the

tumor-to-kidney ratio of radiofolates in mice. The aim of this study was to investigate the dose dependence of these effects and whether the same results could be achieved with folic acid (FA) or 5-methyl-tetrahydrofolate (5-Me-THF). Methods: Biodistribution was assessed 4 h postinjection of the organometallic 99mTc-picolylamine monoacetic acid folate in nude mice bearing FR-pos. KB cell tumor xenografts. PMX (50-400 μg/mouse) was injected 1 h previous to radioactivity. The effects of FA and 5-Me-THF (0.5-50 μg/mouse) were investigated likewise. Tissues and organs were collected and counted for radioactivity and the values tabulated as percentage of injected dose per g tissue (% ID/g). Results: PMX administration reduced renal retention (<1.6% ID/g vs. control: >10% ID/g), while the tumor uptake (average 1.35% ± 0.40% ID/g vs. control: 1.79% ± 0.49% ID/g) was only slightly affected independent of the PMX dose. Replacement of PMX by FA or 5-Me-THF (50 μg/mouse) resulted in a significant renal blockade (<0.1% ID/g) but at the same time in an undesired reduction of tumor uptake (<0.2% ID/g). Conclusions: Selective reduction of radiofolate uptake in kidneys under retention of high tumor accumulation could be achieved in combination with PMX over a broad dose range but not with FA or 5-Me-THF.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2008:400343 CAPLUS

DOCUMENT NUMBER: 149:417018

TITLE: A Randomized Phase II Trial of Pemetrexed plus Irinotecan (ALIRI) versus Leucovorin-Modulated 5-FU plus Irinotecan (FOLFIRI) in First-Line Treatment of Locally Advanced or Metastatic Colorectal Cancer

AUTHOR(S): Underhill, Craig; Goldstein, David; Gorbounova, Vera A.; Biakhov, Mikhail Y.; Bazin, Igor S.; Granov, Dmitry A.; Hossain, Anwar M.; Blatter, Johannes; Kaiser, Christopher; Ma, Doreen

CORPORATE SOURCE: Border Medical Oncology, Wodonga, Vic, Australia

SOURCE: Oncology (2007), 73(1-2), 9-20
CODEN: ONCOBS; ISSN: 0030-2414

PUBLISHER: S. Karger AG

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This multicenter, randomized trial compared overall response rate between pemetrexed plus irinotecan (ALIRI) and leucovorin-modulated 5-fluorouracil plus irinotecan (FOLFIRI) in patients with advanced colorectal cancer. Secondary objectives included overall and progression-free survival, duration of response, toxicities, and biomarkers. ALIRI patients received pemetrexed 500 mg/m2 and irinotecan 350 mg/m2 with vitamin supplementation on day 1 of each 21-day cycle. FOLFIRI patients received irinotecan 180 mg/m2 on days 1, 15, 29; on days 1, 2, 15, 16, 29, 30, patients received leucovorin 200 mg/m2, bolus 5-fluorouracil 400 mg/m2, and 5-fluorouracil 600 mg/m2 as 22-h infusion. Of 132 patients randomly assigned, 130 patients (64 = ALIRI, 66 = FOLFIRI) received ≥1 dose of treatment. Response rates (ALIRI = 20.0%, FOLFIRI = 33.3%) were not significantly different between arms ($p = 0.095$). Progression-free survival was 5.7 mo for ALIRI and 7.7 mo for FOLFIRI ($p < 0.001$). Neutropenia, fatigue, diarrhea, nausea, and vomiting were the major toxicities. There were 5 drug-related deaths (ALIRI = 4, FOLFIRI = 1). Biomarker anal. failed to reveal that any of the 18 preselected genes were clearly associated with tumor response. Neither efficacy nor safety improved on the ALIRI arm compared to the FOLFIRI arm. Progression-free survival on FOLFIRI was significantly longer compared to ALIRI. Potential biomarkers capable of predicting response to either regimen in advanced or metastatic colorectal carcinoma need further characterization.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2006:1343787 CAPLUS
DOCUMENT NUMBER: 146:197623
TITLE: A proposed clinical test for monitoring fluoropyrimidine therapy: detection and stability of thymidylate synthase ternary complexes
AUTHOR(S): Brody, Jonathan R.; Gallmeier, Eike; Yoshimura, Kiyoshi; Hucl, Tomas; Kulesza, Peter; Canto, Marcia I.; Hruban, Ralph H.; Schulick, Richard D.; Kern, Scott E.
CORPORATE SOURCE: Department of Oncology; The Sol Goldman Pancreatic Cancer Research Center and The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
SOURCE: Cancer Biology & Therapy (2006), 5(8), 923-927
CODEN: CBTAAO; ISSN: 1538-4047
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5-Fluorouracil forms classic (covalent, ternary) complexes consisting of thymidylate synthase, fluoro-deoxyuridine monophosphate, and 5, 10-methylene tetrahydrofolate. Despite a high pharmacol. interest in the classic complexes formed in cells treated with fluorouracil anticancer agents, the in vivo stability of the complexes and the possible interference in complex formation by other coadministered compds. have not been adequately described. We visualized classic complexes unaccompanied by unbound thymidylate synthase, inferring complete enzymic inhibition, in 5-fluorouracil-treated S. cerevisiae and cancer cells in vitro and in murine tumors in vivo treated with 5-fluorouracil. Classic complexes persisted 13 days in cancer cells after a pulse of 5-fluorouracil. Classic complexes were reduced to absent in cancer cells in which the older antifolates methotrexate and aminopterin, or the modern antifolates pemetrexed and tomudex, were coadministered with 5-fluorouracil. Classic complexes were, however, detected when an alternate drug, 5-fluorodeoxyuridine, was administered with methotrexate. We visualized classic complexes at fifteen minutes to seven days after an acute single dose of 5-fluorouracil in mouse tumor models, in tumors and normal tissues. Using the same assay, we detected unbound thymidylate synthase in untreated human tissues, supporting the future use of this assay in evaluating the most appropriate dose of fluoropyrimidine and coadministered agents in clin. settings.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2006:485104 CAPLUS
DOCUMENT NUMBER: 145:431762
TITLE: Computer modelling of antifolate inhibition of folate metabolism using hybrid functional petri nets
AUTHOR(S): Assaraf, Yehuda G.; Ifergan, Ilan; Kadry, Wisam N.; Pinter, Ron Y.
CORPORATE SOURCE: Department of Biology, The Technion-Israel Institute of Technology, Technion, Haifa, 32000, Israel
SOURCE: Journal of Theoretical Biology (2006), 240(4), 637-647
CODEN: JTBIAP; ISSN: 0022-5193
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Antifolates are used in the treatment of various human malignancies and exert their cytotoxic activity by inhibiting folate-dependent enzymes resulting in disruption of DNA synthesis and cell death. Here we devised a computerized hybrid functional petri nets (HFPN) modeling of folate metabolism under physiol. and antifolate inhibitory conditions. This HFPN modeling proved valid as a good agreement was found between the simulated steady-state concns. of various reduced folates and those published for cell exts.; consistently, the simulation derived total folate pool size (11.3 μM) was identical to that published for cell exts. In silico expts. were conducted to characterize the inhibitory profile of four distinct antifolates including methotrexate (MTX), tomudex, and LY309887, which inhibit dihydrofolate reductase (DHFR), thymidylate synthase (TS) and glycineamide ribonucleotide transformylase (GARTFase), resp., as well as pemetrexed which has the capacity to inhibit all three enzymes. In order to assess the inhibitory activity of antifolates on purines and pyrimidines, the biosynthesis rates of IMP (20.53 μM/min) and dTMP (23.8 μM/min) were first simulated. Whereas the biochem. inhibitory profile of MTX was characterized by increased dihydrofolate and decreased tetrahydrofolate (THF) concns., the remaining antifolates did not decrease THF levels. Furthermore, MTX was 766- and 10-fold more potent in decreasing the production rates of IMP and dTMP, resp., than pemetrexed. LY309887 indirectly decreased the rate of dTMP production by reducing the levels of 5-CH2-THF, a folate cofactor for TS. Surprisingly, pemetrexed failed to inhibit DHFR even at high concns. This HFPN-based simulation offers an inexpensive, user-friendly, rapid and reliable means of pre-clin. evaluation of the inhibitory profiles of antifolates.

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:588673 CAPLUS

DOCUMENT NUMBER: 143:91000

TITLE: Reduction of toxicity of multi-targeting antifolates

INVENTOR(S): Gustavsson, Bengt; Carlsson, Goeran

PATENT ASSIGNEE(S): Biofol AB, Swed.

SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005060973	A1	20050707	WO 2004-SE1955	20041222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2550298	A1	20050707	CA 2004-2550298	20041222
EP 1699462	A1	20060913	EP 2004-809128	20041222

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS

JP 2007515482 T 20070614 JP 2006-546912 20041222
US 20070249613 A1 20071025 US 2007-583508 20070515
PRIORITY APPLN. INFO.: SE 2003-3526 A 20031222
WO 2004-SE1955 W 20041222
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The use of tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate, and at least one multi-targeting antifolate, for the manufacture of a pharmaceutical composition for the treatment of cancer is disclosed. By combining the multi-targeting anti-folate with tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate , it is possible to remarkably reduce toxic side-effects without diminishing the antitumor action of the drugs. A pharmaceutical composition, a kit comprising the pharmaceutical composition as well as a method for the treatment of cancer are also disclosed. An example is give of multitargeting antifolate therapy in combination the the natural isome of methylenetetrahydrofolate in experiment adenocarcinoma in rats.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1995:338760 CAPLUS
DOCUMENT NUMBER: 122:177869
ORIGINAL REFERENCE NO.: 122:32337a,32340a
TITLE: Multifactorial resistance to 5,10-dideazatetrahydrofolic acid in cell lines derived from human lymphoblastic leukemia CCRF-CEM
AUTHOR(S): Pizzorno, Giuseppe; Moroson, Barbara A.; Cashmore, Arlene R.; Russello, Orsolina; Mayer, Jennifer R.; Galivan, John; Bunni, Marlene A.; Priest, David G.; Beardsley, G. Peter
CORPORATE SOURCE: Dept. Pediatrics, Yale Univ. Sch. of Medicine, New Haven, CT, 06510, USA
SOURCE: Cancer Research (1995), 55(3), 566-73
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5,10-Dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF) is a potent antiproliferative agent in cell culture systems and in vivo in a number of murine and human xenograft tumors. In contrast to classical antifolates, which are dihydrofolate reductase inhibitors, DDATHF primarily inhibits glycinamide ribonucleotide transformylase, the 1st folate-dependent enzyme along the pathway of de novo purine biosynthesis. The (6R) diastereomer of DDATHF (Lometrexol), currently undergoing clin. investigation, was used to develop CCRF-CEM human leukemia sublines resistant to increasing concns. of the drug. Three cell lines were selected for ability to grow in medium containing 0.1 μM, 1.0 μM, and 10 μM (6R)-DDATHF, resp. Impaired polyglutamylation was identified as a common mechanism of resistance in all 3 cell lines. A progressive decrease in the level of polyglutamylation was associated with diminished folylpolyglutamate synthetase activity and paralleled increasing levels of resistance to the drug. However, the expression of folylpolyglutamate synthetase mRNA was not altered in the resistant cell lines compared to the parent cells. The most resistant cell subline also displayed an increased activity of γ-glutamyl hydrolase. The sublines were scrutinized for other possible mechanisms of resistance. No alterations

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     in drug transport or in purine economy were found.  Modest increases were
     found in the activity of methylene tetrahydrofolate
     dehydrogenase but no alterations of other folate-dependent enzymes were
     observed  Increases in accumulation and conversion of folic acid to reduced
     forms, particularly 10-formyltetrahydrofolate, were also seen.  The
     resistant cell lines were sensitive to the dihydrofolate reductase
     inhibitors methotrexate and trimetrexate for a 72-h exposure period but
     showed cross-resistance to methotrexate for 4- and 24-h exposures.
     Cross-resistance was also shown toward other deazafolate analogs for both
     short- and long-term exposures.
OS.CITING REF COUNT:     39     THERE ARE 39 CAPLUS RECORDS THAT CITE THIS
                                RECORD (40 CITINGS)


=> d his

     (FILE 'HOME' ENTERED AT 13:07:18 ON 29 JAN 2010)

     FILE 'REGISTRY' ENTERED AT 13:08:22 ON 29 JAN 2010
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L2             0 S TETRAHYDROFOLATE/CN
                 E "TETRAHYDROFOLATE"/CN 25
                 E "TETRAHYDROFOLIC ACID"/CN 25
L3             1 S E3
                 E "TETRAHYDROFOLIC ACID"/CN 25
                 E "METHYL-TETRAHYDROFOLATE"/CN 25
                 E "5-METHYLTETRAHYDROFOLATE"/CN 25
                 E "5-MTHF"/CN 25
                 E "5,10-METHYLENETETRA"/CN 25
                 E "5,10-METHYLENETETRAHYDROFOLATE"/CN 25
                 E "MTHF"/CN 25
L4             1 S E3

     FILE 'CAPLUS' ENTERED AT 13:13:16 ON 29 JAN 2010
L5          1971 S L3 OR METHYLENE-TETRAHYDROFOLATE OR METHYL-TETRAHYDROFOLATE
L6             8 S L5 AND (PEMETREXED OR RALITREXED OR LOMETREXOL)
L7             8 DUP REM L6 (0 DUPLICATES REMOVED)

=> FIL REGISTRY
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    42.47      75.13

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -6.80      -6.80

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DICTIONARY FILE UPDATES:  27 JAN 2010  HIGHEST RN 1203797-79-8

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http://www.cas.org/support/stngen/stndoc/properties.html

=> E "METHYLENETETRAHYDROFOLATE"/CN 25
E1 2 METHYLENETETRAHYDROFOLAT E REDUCTASE (AGROBACTERIUM TUMEFACIENS
STRAIN C58 GENE METF)/CN
E2 1 METHYLENETETRAHYDROFOLAT E REDUCTASE (METHANOSARCINA MAZEI
STRAIN GOE1 GENE MM0438)/CN
E3 0 --> METHYLENETETRAHYDROFOLATE/CN
E4 1 METHYLENETETRAHYDROFOLATE (NICOTINAMIDE ADENINE DINUCLEOTIDE)
DEHYDROGENASE/CN
E5 1 METHYLENETETRAHYDROFOLATE (REDUCED NICOTINAMIDE ADENINE
DINUCLEOTIDE PHOSPHATE) REDUCTASE/CN
E6 1 METHYLENETETRAHYDROFOLATE (REDUCED NICOTINAMIDE ADENINE
DINUCLEOTIDE) REDUCTASE/CN
E7 1 METHYLENETETRAHYDROFOLATE (REDUCED RIBOFLAVIN ADENINE
DINUCLEOTIDE) REDUCTASE/CN
E8 1 METHYLENETETRAHYDROFOLATE CYCLOHYDROLASE/CN
E9 1 METHYLENETETRAHYDROFOLATE CYCLOHYDROLASE (THIOBACILLUS
DENITRIFICANS STRAIN ATCC 25259)/CN
E10 1 METHYLENETETRAHYDROFOLATE
CYCLOHYDROLASE-METHYLENETETRAHYDROFOLATE DEHYDROGENASE (STREPTOCOCCUS PNEUMONIAE
GENE FOLD)/CN
E11 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE/CN
E12 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (ANAPLASMA MARGINALE
STRAIN ST. MARIES GENE FOLD)/CN
E13 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (AQUIFEX AEOLICUS GENE
FOLD)/CN
E14 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (ARABIDOPSIS THALIANA
GENE AT2G38660)/CN
E15 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (BACILLUS THURINGIENSIS
STRAIN AL HAKAM GENE FOLD)/CN
E16 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (BACTEROIDES FRAGILIS
STRAIN YCH46)/CN
E17 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (BARTONELLA HENSELAE
STRAIN HOUSTON-1 GENE FOLD)/CN
E18 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (BARTONELLA QUINTANA
STRAIN TOULOUSE GENE FOLD)/CN
E19 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (BORRELIA AFZELII STRAIN
PKO GENE FOLD)/CN
E20 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (BORRELIA GARINII STRAIN
PBI GENE FOLD)/CN
E21 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (BUCHNERA APHICICOLA
STRAIN BAIZONGIA PISTACIAE GENE FOLD)/CN
E22 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (CLOSTRIDIUM TETANI
STRAIN E88 GENE CTC01579)/CN
E23 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (CORYNEBACTERIUM
DIPHTHERIAE STRAIN NCTC13129 GENE FOLD)/CN
E24 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (DEHALOCOCCOIDES STRAIN
CBDB1 GENE FOLD)/CN
E25 1 METHYLENETETRAHYDROFOLATE DEHYDROGENASE (DESULFOTALEA
PSYCHROPHILA STRAIN LSV54)/CN

=> d his

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     (FILE 'HOME' ENTERED AT 13:07:18 ON 29 JAN 2010)

     FILE 'REGISTRY' ENTERED AT 13:08:22 ON 29 JAN 2010
L1          3075 S TETRAHYDROFOLATE
L2             0 S TETRAHYDROFOLATE/CN
                 E "TETRAHYDROFOLATE"/CN 25
                 E "TETRAHYDROFOLIC ACID"/CN 25
L3             1 S E3
                 E "TETRAHYDROFOLIC ACID"/CN 25
                 E "METHYL-TETRAHYDROFOLATE"/CN 25
                 E "5-METHYLTETRAHYDROFOLATE"/CN 25
                 E "5-MTHF"/CN 25
                 E "5,10-METHYLENETETRA"/CN 25
                 E "5,10-METHYLENETETRAHYDROFOLATE"/CN 25
                 E "MTHF"/CN 25
L4             1 S E3

     FILE 'CAPLUS' ENTERED AT 13:13:16 ON 29 JAN 2010
L5          1971 S L3 OR METHYLENE-TETRAHYDROFOLATE OR METHYL-TETRAHYDROFOLATE
L6             8 S L5 AND (PEMETREXED OR RALITREXED OR LOMETREXOL)
L7             8 DUP REM L6 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 13:15:04 ON 29 JAN 2010
                 E "METHYLENETETRAHYDROFOLATE"/CN 25

=> s pemetrexed
L8             8 PEMETREXED

=> s ralitrexed
L9             0 RALITREXED

=> s raltitrexed
L10            1 RALTITREXED

=> s lometrexol
L11            2 LOMETREXOL

=> file medline embase biosis
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                23.47      98.60

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                 0.00      -6.80

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COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
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                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    3.33     101.93

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)       SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    0.00      -6.80

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SET COMMAND COMPLETED

SEL L3 1- CHEM
L12         SEL L3 1- CHEM :      12 TERMS

SET SMARTSELECT OFF
SET COMMAND COMPLETED


COST IN U.S. DOLLARS                             SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                   15.49     117.42

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)       SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                    0.00      -6.80

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FILE 'BIOSIS' ENTERED AT 13:16:41 ON 29 JAN 2010
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S L12
L13       2719 L12

=> d his

     (FILE 'HOME' ENTERED AT 13:07:18 ON 29 JAN 2010)

     FILE 'REGISTRY' ENTERED AT 13:08:22 ON 29 JAN 2010
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L2             0 S TETRAHYDROFOLATE/CN
               E "TETRAHYDROFOLATE"/CN 25
               E "TETRAHYDROFOLIC ACID"/CN 25
L3             1 S E3
               E "TETRAHYDROFOLIC ACID"/CN 25
               E "METHYL-TETRAHYDROFOLATE"/CN 25
               E "5-METHYLTETRAHYDROFOLATE"/CN 25
               E "5-MTHF"/CN 25
               E "5,10-METHYLENETETRA"/CN 25
               E "5,10-METHYLENETETRAHYDROFOLATE"/CN 25
               E "MTHF"/CN 25
L4             1 S E3

     FILE 'CAPLUS' ENTERED AT 13:13:16 ON 29 JAN 2010
L5          1971 S L3 OR METHYLENE-TETRAHYDROFOLATE OR METHYL-TETRAHYDROFOLATE
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L6             8 S L5 AND (PEMETREXED OR RALITREXED OR LOMETREXOL)
L7             8 DUP REM L6 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 13:15:04 ON 29 JAN 2010
                E "METHYLENETETRAHYDROFOLATE"/CN 25
L8             8 S PEMETREXED
L9             0 S RALITREXED
L10            1 S RALTITREXED
L11            2 S LOMETREXOL

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:16:34 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:16:40 ON 29 JAN 2010
                SET SMARTSELECT ON
L12           SEL L3 1- CHEM :       12 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:16:41 ON 29 JAN 2010
L13         2719 S L12

=> s l8<chem> or l10<chem> or l11<chem>

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     3.33     120.75

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
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SEL L8 1- CHEM
L14           SEL L8 1- CHEM :       24 TERMS

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    15.49     136.24

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -6.80

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FILE 'EMBASE' ENTERED AT 13:17:09 ON 29 JAN 2010
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S L14 OR L10<CHEM> OR L11<CHEM>

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     3.33     139.57

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
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SEL L10 1- CHEM
L15         SEL L10 1- CHEM :       7 TERMS

SET SMARTSELECT OFF
SET COMMAND COMPLETED


COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    15.49     155.06

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
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S L14 OR L15 OR L11<CHEM>

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     3.33     158.39

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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                                                    ENTRY    SESSION
CA SUBSCRIBER PRICE                                  0.00      -6.80

FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
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SEL L11 1- CHEM
L16         SEL L11 1- CHEM :       6 TERMS

SET SMARTSELECT OFF
SET COMMAND COMPLETED


COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                    ENTRY    SESSION
FULL ESTIMATED COST                                 15.49     173.88

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                    ENTRY    SESSION
CA SUBSCRIBER PRICE                                  0.00      -6.80

FILE 'MEDLINE' ENTERED AT 13:17:11 ON 29 JAN 2010

FILE 'EMBASE' ENTERED AT 13:17:11 ON 29 JAN 2010
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FILE 'BIOSIS' ENTERED AT 13:17:11 ON 29 JAN 2010
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S L14 OR L15 OR L16




L20       8299 L17 OR L18 OR L19

=> s l13 and l20
L21         69 L13 AND L20

=> s l21 and pd<20041222
   2 FILES SEARCHED...
L22         66 L21 AND PD<20041222

=> dup rem l22
PROCESSING COMPLETED FOR L22
L23         47 DUP REM L22 (19 DUPLICATES REMOVED)

=> d l23 1-47 ibib abs

L23  ANSWER 1 OF 47  EMBASE  COPYRIGHT (c) 2010 Elsevier B.V. All rights
     reserved on STN
ACCESSION NUMBER:   2004414900  EMBASE
TITLE:              Characterization of a folate transporter in HeLa cells with
                    a low pH optimum and high affinity for pemetrexed
                    distinct from the reduced folate carrier.
```

AUTHOR: Wang, Yanhua; Zhao, Rongbao; Goldman, I. David (correspondence)
CORPORATE SOURCE: Department of Medicine, Cancer Research Center, Albert Einstein College of Medicine, Bronx, NY, United States. igoldman@aecom.yu.edu
AUTHOR: Goldman, I. David (correspondence)
CORPORATE SOURCE: A. Einstein Coll. Med. Cancer Ctr., Chanin 2, 1300 Morris Park Avenue, Bronx, NY 10461, United States. igoldman@aecom.yu.edu
SOURCE: Clinical Cancer Research, (15 Sep 2004) Vol. 10, No. 18 I, pp. 6256-6264.
Refs: 44
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 21 Oct 2004
Last Updated on STN: 21 Oct 2004

AB Studies were undertaken to characterize a low pH transport activity in a reduced folate carrier (RFC)-null HeLa-derived cell line (R5). This transport activity has a 20-fold higher affinity for pemetrexed (PMX; Kt, .apprx.45 nmol/L) than methotrexate (MTX; Kt .apprx.1 μmol/L) with comparable Vmax values. The Ki values for folic acid, ZD9331, and ZD1694 were .apprx. 400-600 nmol/L, and the Ki values for PT523, PT632, and trimetrexate were >50 μmol/L. The transporter is stereospecific and has a 7-fold higher affinity for the 6S isomer than the 6R isomer of 5-formyltetrahydrofolate but a 4-fold higher affinity for the 6R isomer than the 6S isomer of dideazatetrahydrofolic acid. Properties of RFC-independent transport were compared with transport mediated by RFC at low pH using HepG2 cells, with minimal constitutive low pH transport activity, transfected to high levels of RFC. MTX influx Kt was comparable at pH 7.4 and pH 5.5 (1.7 versus 3.8 μmol/L), but Vmax was decreased 4.5-fold. There was no difference in the Kt for PMX (.apprx.1.2 μmol/L) or the Ki for folic acid (.apprx.130 μmol/L) or PT523 (.apprx.0.2 μmol/L) at pH 7.4 and pH 5.5. MTX influx in R5 and HepG2 transfectants at pH 5.5 was trans-stimulated in cells loaded with 5-formyltetrahydrofolate, inhibited by Cl- (HepG2-B > R5), Na + independent, and uninhibited by energy depletion. Hence, RFC-independent low pH transport activity in HeLa R5 cells is consistent with a carrier-mediated process with high affinity for PMX. Potential alterations in protonation of RFC or the folate molecule as a function of pH do not result in changes in affinity constants for antifolates. Whereas both activities at low pH have similarities, they can be distinguished by folic acid and PT523, agents for which they have very different structural specificities.

L23 ANSWER 2 OF 47 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN
ACCESSION NUMBER: 2007:256964 BIOSIS
DOCUMENT NUMBER: PREV200700278956
TITLE: Selective and complete preservation of pernetrexed pharmacological activity in HeLa cells lacking the reduced folate carrier.
AUTHOR(S): Zhao, Rongbao [Reprint Author]; Hanscom, Marie; Chattopadhyay, Shrikanta; Goldman, I. David
CORPORATE SOURCE: Albert Einstein Coll Med, Bronxville, NY USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (MAR 2004) Vol. 45, pp. 1068.
Meeting Info.: 95th Annual Meeting of the

American-Association-for-Cancer-Research. Orlando, FL, USA. March 27 -31, 2004. Amer Assoc Canc Res.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Apr 2007
Last Updated on STN: 11 Jul 2007

L23 ANSWER 3 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004390293 EMBASE
TITLE: Human reduced folate carrier gene and transcript variants: Functional, physiologic, and pharmacologic consequences.
AUTHOR: Matherly, Larry H. (correspondence)
CORPORATE SOURCE: Barbara Ann Karmanos Cancer Inst., The Department of Pharmacology, Wayne State Univ. School of Medicine, 110 E. Warren Ave., Detroit, MI 48201, United States. matherly@karmanos.org
AUTHOR: Matherly, Larry H. (correspondence)
CORPORATE SOURCE: Exp./Clinical Therapeutics Program, Karmanos Cancer Institute, 110 E. Warren Ave., Detroit, MI 48201, United States. matherly@karmanos.org
SOURCE: Current Pharmacogenomics, (Sep 2004) Vol. 2, No. 3, pp. 287-298.
Refs: 103
ISSN: 1570-1603 CODEN: CPUHAC
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Sep 2004
Last Updated on STN: 30 Sep 2004

AB The primary route for membrane transport of reduced folates into mammalian cells and tissues is the ubiquitously expressed reduced folate carrier (RFC). RFC is also involved in specialized tissue functions related to folates, including absorption across the intestinal epithelium and transplacental transport of folates. This chapter summarizes the current understanding of the major human RFC gene and transcript variants, best typified by G80A that results in a Arg to His substitution at position 27, a functional 61 bp deletion in promoter A, and a CATG insertion at position 191 that results in loss of functional carrier. The occurrence of RFC gene and transcript sequence variants might alter levels of tetrahydrofolate cofactor transport into cells and tissues at the level of modified or decreased RFC, resulting in effects on folate absorption, or downstream effects on folate-dependent biosynthetic pathways. These may contribute to inter-individual differences in susceptibilities to cardiovascular disease, fetal abnormalities, or cancer, particularly in combination with low serum folates. For patients with cancer, treated with antifolate chemotherapy, RFC variants may alter drug pharmacokinetics and antifolate uptake by both tumor and normal cells, thus influencing antitumor activities and toxicities associated with the administration of chemotherapy. Transport defects resulting from changes in RFC structure or expression may be compounded by changes in the catalytic activities of folate-dependent interconverting and biosynthetic enzymes (e.g., 5,10-methylene tetrahydrofolate reductase) that impact cellular distributions of individual tetrahydrofolate forms. By identifying and better understanding naturally occurring RFC gene and transcript variants, it may be possible to develop genetic screens to identify particular

groups of patients who may be predisposed to pathologies resulting from folate deficiencies, or who may be subject to unacceptable toxicities or enhanced antitumor effects of antifolate therapeutics. .COPYRGT. 2004 Bentham Science Publishers Ltd.

L23 ANSWER 4 OF 47 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003281447 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12755606
TITLE: Rational design, synthesis, evaluation, and crystal structure of a potent inhibitor of human GAR Tfase: 10-(trifluoroacetyl)-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic acid.
AUTHOR: Zhang Yan; Desharnais Joel; Marsilje Thomas H; Li Chenglong; Hedrick Michael P; Gooljarsingh Lata T; Tavassoli Ali; Benkovic Stephen J; Olson Arthur J; Boger Dale L; Wilson Ian A
CORPORATE SOURCE: Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA.
CONTRACT NUMBER: P01 CA63536 (United States NCI NIH HHS)
P41 RR08605 (United States NCRR NIH HHS)
R24 CA95830 (United States NCI NIH HHS)
SOURCE: Biochemistry, (2003 May 27) Vol. 42, No. 20, pp. 6043-56.
Journal code: 0370623. ISSN: 0006-2960. L-ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 18 Jun 2003
Last Updated on STN: 3 Jul 2003
Entered Medline: 2 Jul 2003

AB Glycinamide ribonucleotide transformylase (GAR Tfase) has been the target of anti-neoplastic intervention for almost two decades. Here, we use a structure-based approach to design a novel folate analogue, 10-(trifluoroacetyl)-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic acid (10-CF(3)CO-DDACTHF, 1), which specifically inhibits recombinant human GAR Tfase (K(i) = 15 nM), but is inactive (K(i) > 100 microM) against other folate-dependent enzymes that have been examined. Moreover, compound 1 is a potent inhibitor of tumor cell proliferation (IC(50) = 16 nM, CCRF-CEM), which represents a 10-fold improvement over Lometrexol, a GAR Tfase inhibitor that has been in clinical trials. Thus, this folate analogue 1 is among the most potent and selective inhibitors known toward GAR Tfase. Contributing to its efficacious activity, compound 1 is effectively transported into the cell by the reduced folate carrier and intracellularly sequestered by polyglutamation. The crystal structure of human GAR Tfase with folate analogue 1 at 1.98 A resolution represents the first structure of any GAR Tfase to be determined with a cofactor or cofactor analogue without the presence of substrate. The folate-binding loop of residues 141-146, which is highly flexible in both Escherichia coli and unliganded human GAR Tfase structures, becomes highly ordered upon binding 1 in the folate-binding site. Computational docking of the natural cofactor into this and other apo or complexed structures provides a rational basis for modeling how the natural cofactor 10-formyltetrahydrofolic acid interacts with GAR Tfase, and suggests that this folate analogue-bound conformation represents the best template to

date for inhibitor design.

L23 ANSWER 5 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003126334 EMBASE
TITLE: Decreased expression of the reduced folate carrier and folypolyglutamate synthetase is the basis for acquired resistance to the pemetrexed antifolate (LY231514) in an L1210 murine leukemia cell line.
AUTHOR: Wang, Yanhua; Zhao, Rongboa; Goldman, I. David (correspondence)
CORPORATE SOURCE: Dept. of Med./Molecular Pharmacology, Albert Einstein Coll. Med. Cancer C., 1300 Morris Park Avenue, Bronx, NY 10461, United States. igoldman@aecom.yu.edu
SOURCE: Biochemical Pharmacology, (1 Apr 2003) Vol. 65, No. 7, pp. 1163-1170.
Refs: 47
ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Apr 2003
Last Updated on STN: 3 Apr 2003

AB Pemetrexed (LY231514) is a new-generation antifolate that, in its polyglutamyl forms, is a potent inhibitor of thymidylate synthase and glycinamide ribonucleotide formyltransferase (GAR transformylase). This study explored the mechanisms of resistance to pemetrexed in L1210 murine leukemia cells using chemical mutagenesis with 5-formyltetrahydrofolate (5-formylTHF) as the growth substrate. A cell line, MTA-13, was identified that was 8.5-fold resistant to pemetrexed with comparable cross-resistance to ZD1694 (Tomudex) and lesser cross-resistance (5-fold) to ZD9331 [(2S)-2-{O-fluoro-p-[N-(2,7-dimethyl-4-oxo-3,4-dihydro-quinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)-butyric acid], DDATHF (dideazatetrahydrofolate) (3.5-fold), and methotrexate (MTX) (2.7-fold) but comparable sensitivity to trimetrexate. Influx of pemetrexed, MTX, and 5-formylTHF into MTA-13 cells was decreased by 56, 47, and 38% compared to wild-type cells. Folate receptor expression was negligible in both cell lines. Net drug uptake declined within 15min to a slower, constant rate over the next 45 min, reflecting the rate of accumulation of pemetrexed polyglutamate derivatives. This rate in the MTA-13 line was half that of the wild-type cells. Accumulation of 50 nM [3H]pemetrexed, 25 nM [3H]5-formylTHF, or 50 nM [3H]DDATHF after 3 days was decreased to 35, 46, and 56% the level of L1210 cells. The reduced folate carrier (RFC) message and protein were decreased by 50%, and folypolyglutamate synthetase (FPGS) message was decreased by 65% in MTA-13 cells. No mutations were detected in either protein by DNA sequence analysis. There was a slight decrease (.apprx.25%) in thymidylate synthase mRNA, without mutations in the protein, and there was no change in GAR transformylase message. The data indicate that resistance to pemetrexed in the MTA-13 cell line was due to changes in both RFC and FPGS expression, two proteins that act in tandem to regulate polyglutamation of folates and antifolates in cells, resulting in cellular depletion of these active pemetrexed congeners. .COPYRGT. 2003 Elsevier Science Inc. All rights reserved.

L23 ANSWER 6 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights

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ACCESSION NUMBER: 2002247861 EMBASE
TITLE: Pemetrexed (Alimta.RTM.): A novel antifolate in the treatment of malignant pleural mesothelioma.
AUTHOR: Maung, Kavita; Belani, Chandra P.; Jain, Vinay K.
SOURCE: Clinical Lung Cancer, (2002) Vol. 3, No. 4, pp. 240-242.
Refs: 12
ISSN: 1525-7304 CODEN: CLCLCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
030 Clinical and Experimental Pharmacology
035 Occupational Health and Industrial Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Jul 2002
Last Updated on STN: 25 Jul 2002

L23 ANSWER 7 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001407973 EMBASE
TITLE: Single nucleotide polymorphisms in the human reduced folate carrier: Characterization of a high-frequency G/A variant at position 80 and transport properties of the His27 and Arg27 carriers.
AUTHOR: Whetstine, J.R.; Gifford, A.J.; Witt, T.; Liu, X.Y.; Flatley, R.M.; Norris, M.; Haber, M.; Taub, J.W.; Ravindranath, Y.; Matherly, L.H. (correspondence)
CORPORATE SOURCE: Exp. and Clinic. Therapeutics Prog., Karmanos Cancer Institute, 110 East Warren Avenue, Detroit, MI 48201, United States. matherly@kci.wayne.edu
SOURCE: Clinical Cancer Research, (2001) Vol. 7, No. 11, pp. 3416-3422.
Refs: 43
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Dec 2001
Last Updated on STN: 6 Dec 2001

AB The presence of sequence variants in the human reduced folate carrier (hRFC) was assessed in leukemia blasts from children with acute lymphoblastic leukemia (ALL) and in normal peripheral blood specimens. A CATG frame shift insertion at position 191 was detected in 10-60% of hRFC transcripts from 10 of 16 ALL specimens, by RFLP analysis and direct sequencing of hRFC cDNAs. In genomic DNAs prepared from 105 leukemia (n = 54) and non-leukemia (n = 51) specimens, PCR amplifications and direct sequencing of exon 3 identified a high-frequency G to A single nucleotide polymorphism at position 80 that resulted in a change of arginine-27 to histidine-27. The allelic frequencies of G/A80 were nearly identical for the non-leukemia (42.2% CGC and 57.8% CAC) and leukemia (40.7% CGC and 59.3% CAC) genomic DNAs. In cDNAs prepared from 10 of these ALL patients, identical allelic frequencies (40 and 60%, respectively) were recorded.

In up to 62 genomic DNAs, hRFC-coding exons 4-7 were PCR-amplified and sequenced. A high-abundance C/T696 polymorphism was detected with nearly identical frequencies for both alleles, and a heterozygous C/A1242 sequence variant was identified in two ALL specimens. Both C/T696 and C/A1242 were phenotypically silent. In transport assays with [3H]methotrexate and [3H]5-formyl tetrahydrofolate, nearly identical uptake rates were measured for the arginine-27- and histidine-27-hRFC proteins expressed in transport-impaired K562 cells. Although there were no significant differences between the kinetic parameters for methotrexate transport for the hRFC forms, minor (.apprx.2-fold) differences were measured in the Kis for other substrates including Tomudex, 5,10-dideazatetrahydrofolate, GW1843U89, and 10-ethyl-10-deazaaminopterin and for 5-formyl tetrahydrofolate.

L23 ANSWER 8 OF 47 MEDLINE on STN
ACCESSION NUMBER: 2001372722 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11428931
TITLE: Synthesis and biological activity of 7-oxo substituted analogues of 5-deaza-5,6,7, 8-tetrahydrofolic acid (5-DATHF) and 5,10-dideaza-5,6, 7,8-tetrahydrofolic acid (DDATHF).
AUTHOR: Borrell J I; Teixido J; Matallana J L; Martinez-Teipel B; Colominas C; Costa M; Balcells M; Schuler E; Castillo M J
CORPORATE SOURCE: Departament de Quimica Organica, Institut Quimic de Sarria, Universitat Ramon Llull, Via Augusta 390, E-08017 Barcelona, Spain.
SOURCE: Journal of medicinal chemistry, (2001 Jul 5) Vol. 44, No. 14, pp. 2366-9.
Journal code: 9716531. ISSN: 0022-2623. L-ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 23 Jul 2001
Last Updated on STN: 23 Jul 2001
Entered Medline: 19 Jul 2001

AB We recently described the syntheses of 12a-c, 4-amino-7-oxo substituted analogues of 5-deaza-5,6,7,8-tetrahydrofolic acid (5-DATHF), and 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF), in six steps from commercially available p-substituted methyl benzoates in 20-27% overall yields. Such analogues were tested in vitro against CCRF-CEM leukemia cells and showed that they are completely devoid of any activity, the IC(50) being higher than 20 microg/mL for all cases. To clarify if the presence of the carbonyl group in position C7, the distinctive feature of our synthetic methodology, is the reason for this lack of activity, we have now obtained the 7-oxo substituted analogues of 5-DATHF and DDATHF, 18a-c, in 10-30% overall yield. Testing of 18a-c in vitro against CCRF-CEM leukemia cells revealed that these compounds are totally inactive. A molecular modeling study of 18b inside the active site of the complex E. coliGARTFase-5-DATHF-GAR pointed to an electronic repulsion between the atoms of the 7-oxo group and the carbonyl group of Arg90 as a possible explanation for the inactivity of 18a-c.

L23 ANSWER 9 OF 47 EMBASE
ACCESSION NUMBER: 2001202350 EMBASE

TITLE: Update on antifolate drugs targets.
AUTHOR: Costi, M.P. (correspondence); Ferrari, S.
CORPORATE SOURCE: Dipartimento di Sci. Farmaceutiche, University of Modena/Reggio Emilia, via Campi 183, 41100 Modena, Italy. costimp@unimo.it
SOURCE: Current Drug Targets, (2001) Vol. 2, No. 2, pp. 135-166.
Refs: 106
ISSN: 1389-4501 CODEN: CDTUAU
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
004 Microbiology: Bacteriology, Mycology, Parasitology and Virology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Jul 2001
Last Updated on STN: 10 Jul 2001

AB Antifolate drugs are molecules directed to interfere with the folate metabolic pathway at some level. They can be recognized among the first rationally designed compounds applying the principle of structural analogy with the substrate developing the antimetabolite strategy. This strategy has taken advantage of the basic different features of the microbial and human folate metabolism and therefore allows targeting the pathway at different steps generating a specificity tools for Medicinal Chemists. Two main problems are giving renewed importance to such targets and therefore improving the efforts to discover new targets in the folate metabolism area. The first one is the increasing resistance to the present drugs due to different mechanisms such as the enzyme modification and the increased production of enzymes with not well recognized importance. The second one is the development of techniques directed to highlight the interference at genetic level of molecular probes as antifolate drug to develop new enzymes previously unknown. This approach is defined as genetic approach to drug discovery, from gene to drugs. The present article describes the importance in drug design and discovery of some antifolate targets among the best known at the present status of research such as thymidylate synthase (TS), dhydrofolate reductases, (DHFR) serine hydroxymethyltransferase (SHMT), folyilpolyglutamyl synthetase (FPGS), γ-glutamyl hydrolase (γ-GH), glycinamide-ribonucleotide transformylase (GARTfase), amino-imidazole-carboxamide-ribonucleotide transformylase (AICARTfase) and Folate transporters. Discovery, known functions, structure/function studies and inhibition will be described.

L23 ANSWER 10 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001080339 EMBASE
TITLE: Schedule-dependent synergism and antagonism between raltitrexed ("Tomudex") and methotrexate in human colon cancer cell lines in vitro.
AUTHOR: Kano, Y. (correspondence); Akutsu, M.; Tsunoda, S.; Suzuki, K.; Yazawa, Y.; Furukawa, Y.
CORPORATE SOURCE: Divisions of Medical Oncology, Tochigi Cancer Center, 4-9-13 Yonan, Utsunomiya, Tochigi 320-0834, Japan. ykano@tcc.pref.tochigi.jp
SOURCE: Japanese Journal of Cancer Research, (2001) Vol. 92, No. 1, pp. 74-82.
Refs: 27
ISSN: 0910-5050 CODEN: JJCREP
COUNTRY: Japan

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Mar 2001
Last Updated on STN: 16 Mar 2001

AB The folate-dependent enzymes are attractive targets for cancer chemotherapy. Methotrexate (MTX), which inhibits dihydrofolate reductase, has been widely used for the treatment of solid tumors and hematological cancers. Raltitrexed ("Tomudex"), which inhibits thymidylate synthase, is a novel anticancer agent active against colorectal cancer and some other solid tumors. We studied the optimal schedule of raltitrexed and MTX in combination against four human colon cancer cell lines Colo201, Colo320, LoVo, and WiDr. These cells were simultaneously exposed to raltitrexed and MTX for 24 h, or sequentially exposed to raltitrexed for 24 h followed by MTX for 24 h, or vice versa. Cell growth inhibition after 5 days was determined by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The effects of drug combinations at the concentrations of drug that produced 80% and 50% cell growth inhibition (IC80 and IC50) were analyzed by the isobologram method (Steel and Peckham, 1979). Cytotoxic interactions between raltitrexed and MTX were schedule-dependent. The simultaneous exposure to raltitrexed and MTX showed additive effects in Colo201, LoVo and WiDr cells and antagonistic effects in Colo320 cells. The sequential exposure to raltitrexed followed by MTX produced additive effects in all four cell lines. The sequential exposure to MTX followed by raltitrexed produced synergistic effects in Colo201, LoVo and WiDr cells and additive effects in Colo320 cells. These findings suggest that the sequential administration of MTX followed by raltitrexed produces more than the expected cytotoxicity and may be the optimal schedule at the cellular level. Further in vivo and clinical studies will be necessary to determine the toxicity and to test the antitumor effects of sequential administration of MTX followed by raltitrexed proposed on the basis of the in vitro synergism.

L23 ANSWER 11 OF 47 EMBASE
ACCESSION NUMBER: 2000107979 EMBASE
TITLE: Synergistic interactions among antifolates.
AUTHOR: Kisliuk, Roy L. (correspondence)
CORPORATE SOURCE: Department of Biochemistry, Tufts Univ., 136 Harrison A., Boston, MA, United States. rkisliuk@opal.tufts.edu
AUTHOR: Kisliuk, Roy L. (correspondence)
CORPORATE SOURCE: Department of Biochemistry, Tufts University, 136 Harrison Avenue, Boston, MA 02111, United States. rkisliuk@opal.tufts.edu
SOURCE: Pharmacology and Therapeutics, (Mar 2000) Vol. 85, No. 3, pp. 183-190.
Refs: 20
ISSN: 0163-7258 CODEN: PHTHDT
PUBLISHER IDENT.: S 0163-7258(99)00056-X
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 016 Cancer
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Apr 2000
Last Updated on STN: 6 Apr 2000

AB Many cultured human cell lines show large synergistic cytotoxicity when an inhibitor of dihydrofolate reductase (EC 1.5.1.3) is combined with an antifolate inhibitor of thymidylate synthase (EC 2.1.1.45) or with an antifolate inhibitor of glycinamide ribonucleotide formyltransferase (EC 2.1.2.2). These synergistic interactions are dependent on medium folic acid concentration and are greatly enhanced by increasing folic acid levels. Synergism is seen only when the thymidylate synthase or glycinamide ribonucleotide formyltransferase inhibitor is polyglutamylatable. Here we will briefly outline the rigorous method used to quantitate synergistic interactions by measuring α, a response surface-based parameter; give examples of synergistic interactions from the current literature; and evaluate proposals offered to explain the metabolic basis of the synergism. Copyright (C) 2000 Elsevier Science Inc.

L23 ANSWER 12 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1999369126 EMBASE
TITLE: Synthesis of γ-[15N]-L-glutamyl derivatives of 5,10-dideazatetrahydrofolate.
AUTHOR: Forsch, Ronald A.; Rosowsky, Andre (correspondence)
CORPORATE SOURCE: Dana-Farber Cancer Institute, Dept. Biol. Chem. Molec. Pharmacol., Harvard Medical School, Boston, MA 02115, United States.
AUTHOR: Rosowsky, Andre (correspondence)
CORPORATE SOURCE: Dept. Biolog. Chem. Mol. Pharmacol., Harvard Medical School, Boston, MA 02115, United States.
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals, (1999) Vol. 42, No. 11, pp. 1103-1117.
Refs: 39
ISSN: 0362-4803 CODEN: JLCRD4
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 023 Nuclear Medicine
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Nov 1999
Last Updated on STN: 12 Nov 1999

AB A synthesis of the mono-, di-, and tri[15N]glutamate forms of the potent de novo purine synthesis inhibitor and anticancer agent (6R,6S)-5,10-dideaza-5,6,7,8-tetrahydrofolate (6R,6S-DDATHF) from (6R,6S)-5,10-dideaza-5,6,7,8-tetrahydropteroic acid is described. These isotopically labelled compounds are potentially useful as 15N nmr probes of the interaction of DDATHF and its polyglutamates with three key enzymes of one-carbon metabolism, glycinamide ribonucleotide formyltransferase, (GARFT), aminoimidazolecarboxamide formyltransferase (AICARFT), and folylpolylglutamate synthetase (FPGS).

L23 ANSWER 13 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1999126887 EMBASE
TITLE: Multiple mechanisms of resistance to polyglutamatable and lipophilic antifolates in mammalian cells: Role of increased folylpolyglutamylation, expanded folate pools, and intralysosomal drug sequestration.
AUTHOR: Jansen, Gerrit; Kathmann, Ietje; Noordhuis, Paul; Peters,

Godefridus J.
CORPORATE SOURCE: Department of Oncology, Section of Biochemical Pharmacology, Univ. Hospital Vrije Universiteit, Amsterdam, Netherlands.
AUTHOR: Bunni, Marlene A.; Priest, David G.
CORPORATE SOURCE: Dept. of Biochem. and Molec. Biology, Medical University of South Carolina, Charleston, SC, United States.
AUTHOR: Barr, Haim; Assaraf, Yehuda G., Dr. (correspondence)
CORPORATE SOURCE: Department of Biology, Technion-Israel Inst. of Technology, Haifa 32000, Israel. assaraf@tx.technion.ac.il
SOURCE: Molecular Pharmacology, (1999) Vol. 55, No. 4, pp. 761-769.
Refs: 40
ISSN: 0026-895X CODEN: MOPMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 May 1999
Last Updated on STN: 10 May 1999
AB Chinese hamster ovary Pyr(R100) cells display more than 1000-fold resistance to pyrimethamine (Pyr), a lipophilic antifolate inhibitor of dihydrofolate reductase. Pyr(R100) cells had wild-type DHFR activity, lost folate exporter activity, and had a 4-fold increased activity of a low pH folic acid transporter. Here we report on the marked alterations identified in Pyr(R100) cells compared with parental cells: 1) 100-fold decreased folic acid growth requirement; 2) a 25-fold higher glucose growth requirement in Pyr-containing medium; 3) a 2.5- to 4.1-fold increase in folylpolyglutamate synthetase activity; 4) a 3-fold increase in the accumulation of [3H]folic acid and a 3-fold expansion of the intracellular folate pools; 5) a 4-fold increase in the activity of the lysosomal marker β-hexoseaminidase, suggesting an increased lysosome number/Pyr(R100) cell; and 6) a small reduction in the steady-state accumulation of [3H]Pyr and no evidence of catabolism or modification of cellular [3H]Pyr. Consequently, Pyr(R100) cells were markedly resistant to the lipophilic antifolates trimetrexate (40-fold) and AG377 (30-fold) and to the polyglutamatable antifolates 5, 10-Dideaza-5, 6,7,8-tetrahydrofolic acid (DDATHF) (26-fold) and AG2034 (14-fold). Resistance to these drugs was reversed in Pyr(R100) cells transferred into folate-depleted medium. In conclusion, these multiple resistance factors collectively result in a prominent increase in folate accumulation, an expansion of the intracellular folylpolyglutamate pool, and abolishment of the cytotoxic activity of polyglutamatable and lipophilic antifolates. The role of increased lysosome number per cell in sequestration of hydrophobic weak base drugs such as Pyr is also discussed as a novel mechanism of drug resistance.

L23 ANSWER 14 OF 47 EMBASE
ACCESSION NUMBER: 1999169732 EMBASE
TITLE: The medical treatment of colorectal cancer: Actual status and new developments.
AUTHOR: Van Cutsem, Eric, Dr. (correspondence); Peeters, Marc; Verslype, Chris; Janssens, Jozef
CORPORATE SOURCE: Department of Internal Medicine, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium.
AUTHOR: Filez, Ludo
CORPORATE SOURCE: Department of Surgery, University Hospital Gasthuisberg, Leuven, Belgium.

AUTHOR: Haustermans, Karin
CORPORATE SOURCE: Department of Radiotherapy, University Hospital Gasthuisberg, Leuven, Belgium.
SOURCE: Hepato-Gastroenterology, (1999) Vol. 46, No. 26, pp. 709-716.
Refs: 31
ISSN: 0172-6390 CODEN: HEGAD4
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 009 Surgery
048 Gastroenterology
038 Adverse Reactions Titles
037 Drug Literature Index
030 Clinical and Experimental Pharmacology
016 Cancer
014 Radiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 May 1999
Last Updated on STN: 27 May 1999

AB Colorectal cancer is one of the most frequent malignancies and one of the greatest causes of cancer death in the Western world. The prognosis is determined by the stage at diagnosis. Patients with metastatic colon cancer have a bad prognosis. Chemotherapeutic treatment with 5-Fluorouracil (5-FU) and folinic acid is actually considered as the standard treatment in patients with metastatic disease. Although the survival benefit is relatively small, many patients can benefit from this treatment in terms of tumor regression or symptom improvement. Several new drugs are actually in development and create hope for improved tumor or symptom control and longer survival. Thymidylate synthase inhibitors (raltitrexed), topoisomerase I inhibitors (irinotecan), the oral 5-FU prodrugs (capecitabine, UFT), ethynyluracil, and oxaliplatin are promising new drugs. The challenge will be to determine the best combination of these new drugs and the exact sequence in which these drugs will be used. Adjuvant post-operative chemotherapy in colon cancer is one of the most important advances in oncology that has been introduced into the clinic during the last years. For rectal cancer, an adjuvant treatment should consist of a combined chemo-radiotherapy. The search for better prognostic factors for recurrence should help to focus on a better adjuvant treatment for patients with the highest risk for recurrence.

ACCESSION NUMBER: 1999013909 EMBASE
TITLE: Synthesis of N-{[4-(2-amino-4(3H)-oxo-5,6,7,8-tetrahydro-(9H)- pyrimido[4,5-b]-azepin-6-yl)methyl]benzoyl}-L-glutamic acid and two of its conformationally-restricted analogs.
AUTHOR: Read, Mark W.; Miller, Michael L.; Ray, Partha S. (correspondence)
CORPORATE SOURCE: Department of Chemistry, The University of Memphis, Memphis,TN 38152, United States. psray@memphis.edu
AUTHOR: Ray, Partha S. (correspondence)
CORPORATE SOURCE: Department of Chemistry, University of Memphis, Memphis, TN 38152, United States. psray@memphis.edu
SOURCE: Tetrahedron, (8 Jan 1999) Vol. 55, No. 2, pp. 373-392.
Refs: 26
ISSN: 0040-4020 CODEN: TETRAB
PUBLISHER IDENT.: S 0040-4020(98)01060-6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Feb 1999
Last Updated on STN: 4 Feb 1999

AB Synthesis of the titled tetrahydropyrimidoazepine-based folate (6a) is described using a regiospecific γ-alkylation reaction between the dienolate generated from 3-carboethoxy-N-2,4-dimethoxybenzyl-1,5,6,7-tetrahydro-(1H)- azepin-2-one (33) and methyl 4-formylbenzoate, as the key step. The isoxazolinopyrimidoazepine and isoxazolopyrimidoazepine-based folates (7a and 8a respectively) were also prepared (via intramolecular 1,3-dipolar cycloaddition chemistry) as conformationally-restricted analogs of 6a. All three compounds were prepared as potential antitumor agents based on the known, structurally related, antitumor agent 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF). Both 7a and 8a were inactive in the human colon carcinoma (GC3c1) cell culture assay. Compound 6a, however, was weakly active (IC50 = 2.0 μM) in the above assay.

L23 ANSWER 16 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1999164963 EMBASE
TITLE: Accumulation of plasma reduced folates after folic acid administration.
AUTHOR: Priest, D.G., Dr. (correspondence); Schmitz, J.C.; Bunni, M.A.
CORPORATE SOURCE: Dept. of Biochemistry/Molec. Biol., Medical University of South Carolina, 171 Ashley Ave, Charleston, SC 29425, United States.
SOURCE: Seminars in Oncology, (1999) Vol. 26, No. 2 SUUPL., pp. 38-41.
Refs: 15
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jun 1999
Last Updated on STN: 3 Jun 1999

AB The pharmacokinetics of folic acid, and resultant metabolites thereof, have been determined after administration orally and intravenously at 25 mg/m2 and 125 mg/m2. Saturation behavior was observed for uptake of folic acid into plasma and with regard to metabolism to methylenetetrahydrofolate and tetrahydrofolate as well as methyltetrahydrofolate. Repetitive oral administration every 6 hours resulted in consistently elevated levels of each metabolite pool with the same general saturation behavior as observed with single dose administration. This repetitive oral administration is concluded to be a suitable means to provide uniform elevation of metabolites that could offer protection from undesirable toxic effects of drugs such as MTA.

L23 ANSWER 17 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1999164961 EMBASE
TITLE: Roles of folylpoly-γ-glutamate synthetase in therapeutics with tetrahydrofolate antimetabolites: An overview.

AUTHOR: Moran, R.G., Dr. (correspondence)
CORPORATE SOURCE: Massey Cancer Center, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298-0230, United States.
SOURCE: Seminars in Oncology, (1999) Vol. 26, No. 2 SUUPL., pp. 24-32.
Refs: 50
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jun 1999
Last Updated on STN: 3 Jun 1999

AB Folylpoly-γ-glutamate synthetase (FPGS) catalyzes the addition of several equivalents of glutamic acid to the γ-carboxyl group in the side chain of folate cofactors and analogs. Folylpoly-γ-glutamate synthetase has three functions in folate homeostasis in mammals: polyglutamation prevents efflux of folate cofactors from the cell, it increases the binding of folate cofactors to some of the enzymes of folate interconversion and biosynthesis, and it appears to allow the accumulation of folates in the mitochondria that are required for glycine synthesis. The efficient substrate activity of the newer generations of tetrahydrofolate analogs results in levels of intracellular accumulation of cytotoxic drug in any cell expressing FPGS in which the enzyme activity is not suppressed by feedback, and the binding of folate inhibitors of thymidylate synthase and glycinamide ribonucleotide formyltransferase is substantially increased by polyglutamation. Resistance to these drugs appears to be most frequently due to mutations that change the level of polyglutamation of parent compound, a clear indication of the centrality of the process to the cytotoxicity of these drugs. Folylpoly-γ-glutamate synthetase is widely expressed in human tumors and is tightly linked either to proliferation or to a lack of differentiation. The cytotoxicity of both thymidylate synthase and purine inhibitors requires continued inhibition of target for greater than one generation time, so that the integrative function of FPGS adds considerably to the efficiency of folate antimetabolites.

L23 ANSWER 18 OF 47 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 1998387883 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9719607
TITLE: Synthesis and biological activity of 4-amino-7-oxo-substituted analogues of 5-deaza-5, 6,7,8-tetrahydrofolic acid and 5,10-dideaza-5, 6, 7,8-tetrahydrofolic acid.
AUTHOR: Borrell J I; Teixido J; Martinez-Teipel B; Matallana J L; Copete M T; Llimargas A; Garcia E
CORPORATE SOURCE: Departament de Quimica Organica, Institut Quimic de Sarria, Universitat Ramon Llull, Via Augusta 390, E-08017 Barcelona, Spain.
SOURCE: Journal of medicinal chemistry, (1998 Aug 27) Vol. 41, No. 18, pp. 3539-45.
Journal code: 9716531. ISSN: 0022-2623. L-ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 25 Sep 1998
Last Updated on STN: 25 Sep 1998
Entered Medline: 17 Sep 1998

AB The 4-amino-7-oxo-substituted analogues of 5-deaza-5,6,7,8-tetrahydrofolic acid (5-DATHF) and 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF) were synthesized as potential antifolates. Treatment of the alpha,beta-unsaturated esters 11a-c, obtained in one synthetic step from commercially available para-substituted methyl benzoates (9a-c) and methyl 2-(bromomethyl)acrylate (10), with malononitrile in NaOMe/MeOH afforded the corresponding pyridones 12a-c. Formation of the pyrido[2,3-d]pyrimidines 13a-c was accomplished upon treatment of 12a-c with guanidine in methanol. After the hydrolysis of the ester group present in 13a-c, the resulting carboxylic acids 14a-c were treated with diethyl cyanophosphonate in Et3N/DMF and coupled with L-glutamic acid dimethyl ester to give 15a-c. Finally, the basic hydrolysis of 15a-c yielded the desired 4-amino-7-oxo-substituted analogues 16a-c in 20-27% overall yield. Compounds 16a-c were tested in vitro against CCRF-CEM leukemia cells. The results obtained indicated that our 4-amino-7-oxo analogues are completely devoid of any activity, the IC50 being higher than 20 microg/mL for all cases except 14c for which a value of 6.7 microg/mL was obtained. These results seem to indicate that 16a-c are inactive precisely due to the presence of the carbonyl group in position C7, the distinctive feature of our synthetic methodology.

L23 ANSWER 19 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1997059409 EMBASE
TITLE: Synthesis of a pyrimido[4,5-b]azepine analog of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF).
AUTHOR: Taylor, Edward C. (correspondence); Dowling, James E.
CORPORATE SOURCE: Department of Chemistry, Princeton University, Princeton, NJ 08544, United States.
SOURCE: Bioorganic and Medicinal Chemistry Letters, (18 Feb 1997) Vol. 7, No. 4, pp. 453-456.
Refs: 19
ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.: S 0960-894X(97)00041-3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 1997
Last Updated on STN: 24 Mar 1997

AB The synthesis and biological evaluation of a pyrimido[4,5-b]azepine-based analog of DDATHF, a potential chemotherapeutic agent, are described.

L23 ANSWER 20 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1998018583 EMBASE
TITLE: Folate and antifolate pharmacology.
AUTHOR: Kamen, B., Dr. (correspondence)
CORPORATE SOURCE: Department of Pediatrics, University of Texas, Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX

75235-9063, United States.
SOURCE: Seminars in Oncology, (1997) Vol. 24, No. 5
SUPPL. 18, pp. S18-30-S18-39.
Refs: 71
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Feb 1998
Last Updated on STN: 12 Feb 1998

AB Folio acid is a water-soluble vitamin associated with the other B vitamins. In its fully reduced form (tetrahydrofolate), folate serves as a I- carbon donor for synthesis of purines and thymidine as well as in the remethylation cycle of homocysteine to methionine. Folate is essential for normal cell growth and replication. It therefore is not surprising that folate analogues have served and continue to serve well as antibiotics and cytotoxic drugs in the treatment of cancer, autoimmune diseases, psoriasis, and bacterial and protozoal infections. During the past 50 years, many of the enzymes requiring folate as a co-factor (ie, thymidylate synthase), and molecules critical in folate homeostasis (ie, the reduced folate carrier, folylpolyglutamate synthase), have been purified and even crystallized. The genes have been cloned, sequenced, and mapped, providing detailed knowledge of their regulation and three-dimensional structure. This has, in part, led to the rational synthesis of a large number of folate analogues that differ from methotrexate, the 'classical antifolate,' in transport, metabolism, and intracellular targets. Currently, several new folate analogues with unique biochemical properties and clinical applications are being tested. The goals of this brief review are to review folate homeostasis, to highlight the similarities and differences between natural folate and antifolates with respect to biochemistry and metabolism, and to present the pharmacology of methotrexate and several next-generation folate analogues, such as trimetrexate and raltritrexed, with an emphasis on mechanisms of drug resistance.

L23 ANSWER 21 OF 47 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 1997117098 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8958183
TITLE: A simplified and efficient synthesis of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF).
AUTHOR: Taylor E C; Chaudhari R; Lee K
CORPORATE SOURCE: Department of Chemistry, Princeton University, NJ 08544, USA.
SOURCE: Investigational new drugs, (1996) Vol. 14, No. 3, pp. 281-5.
Journal code: 8309330. ISSN: 0167-6997. L-ISSN: 0167-6997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 24 Apr 1997
Last Updated on STN: 24 Apr 1997
Entered Medline: 14 Apr 1997

AB A new and extremely efficient synthesis of DDATHF from 4-vinylbenzoic acid and bromomalondialdehyde as precursors has been developed which proceeds

in 48% overall yield.

L23 ANSWER 22 OF 47 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1999034965 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9815947
TITLE: Clinical pharmacokinetics of the antipurine antifolate (6R)-5,10- dideaza-5,6,7, 8-tetrahydrofolic acid (Lometrexol) administered with an oral folic acid supplement.
AUTHOR: Wedge S R; Laohavinij S; Taylor G A; Boddy A; Calvert A H; Newell D R
CORPORATE SOURCE: Cancer Research Unit, The Medical School, University of Newcastle-upon-Tyne, Framlington Place, Newcastle-upon-Tyne, NE2 4HH, United Kingdom.
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (1995 Dec) Vol. 1, No. 12, pp. 1479-86.
Journal code: 9502500. ISSN: 1078-0432. L-ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 23 Feb 1999
Last Updated on STN: 23 Feb 1999
Entered Medline: 9 Feb 1999

AB (6R)-5,10-Dideaza-5,6,7,8-tetrahydrofolic acid (lometrexol) is an antipurine antifolate which selectively inhibits glycinamide ribonucleotide formyltransferase. Lometrexol pharmacokinetics were evaluated in 17 patients (32 courses) as part of a Phase I study in which folic acid supplementation was used to improve tolerance to the drug, its clinical utility being previously limited by severe cumulative toxicity. Lometrexol was administered as an i.v. bolus every 4 weeks at a starting dose of 12 mg/m2, with subsequent interpatient dose escalation to 16, 30, and 45 mg/m2. p.o. folic acid (5 mg/day) was given for 7 days before and 7 days after lometrexol administration. The disposition of total lometrexol in plasma was best described by a biexponential model for data acquired up to 12 h after drug administration, although triexponential plasma pharmacokinetics were often found to give a more adequate description when data were available at later time intervals (24 h and greater). Mean plasma half-lives (+ SD) for model-dependent analysis were t1/2alpha 19 +/- 7 min, t1/2beta 256 +/- 96 min, and t1/2gamma (where measurable) 1170 +/- 435 min. Lometrexol area under plasma concentration versus time curve was proportional to the dose administered. Moderate plasma protein binding of lometrexol was evident (78 +/- 3%) with an inverse linear relationship between fraction of unbound lometrexol and the concentration of serum albumin. The volume of distribution of lometrexol at steady state was between 4.7 and 15.8 l/m2. Renal elimination of lometrexol, studied in 19 patients (21 courses), was considerable, accounting for 56 +/- 17% of the total dose administered within 6 h of treatment, and 85 +/- 16% within 24 h of treatment. These recoveries of unchanged lometrexol indicate that the drug does not appear to undergo appreciable systemic metabolism at the range of concentrations studied. Lometrexol pharmacokinetics were also examined in seven patients who received 45 or 60 mg/m2 lometrexol as part of a separate study of the drug given with folinic acid rescue 5-7

days after treatment. No marked differences were evident in lometrexol plasma half-lives, plasma clearance, or the extent of plasma protein binding, indicating that there is not a pronounced pharmacokinetic interaction between lometrexol and folic acid.

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ACCESSION NUMBER: 1995214725 EMBASE
TITLE: Inhibitors of thymidylate synthase and glycinamide ribonucleotide transformylase.
AUTHOR: Jackson, R.C. (correspondence)
CORPORATE SOURCE: Agouron Pharmaceuticals, Inc., San Diego, CA 92121, United States.
SOURCE: Advances in Experimental Medicine and Biology, (1995) Vol. 370, pp. 179-184.
ISSN: 0065-2598 CODEN: AEMBAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Aug 1995
Last Updated on STN: 9 Aug 1995

L23 ANSWER 24 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN DUPLICATE 5

ACCESSION NUMBER: 1994376968 EMBASE
TITLE: Synthesis of 10-(hydroxymethyl)-5,10-dideaza-5,6,7,8-tetrahydrofolic acid, a potent new analogue of DDATHF (Lometrexol).
AUTHOR: Taylor, E.C. (correspondence); Yoon, C.
CORPORATE SOURCE: Department of Chemistry, Princeton University, Princeton, NJ 08544, United States.
SOURCE: Journal of Organic Chemistry, (1994) Vol. 59, No. 23, pp. 7096-7098.
ISSN: 0022-3263 CODEN: JOCEAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jan 1995
Last Updated on STN: 12 Jan 1995
AB A synthesis of 10-(hydroxymethyl)-5,10-dideaza-5,6,7,8-tetrahydrofolic acid [as a mixture of four diastereomers] is described. Substantial cytotoxicity was observed for this new analogue of DDATHF (Lometrexol).

L23 ANSWER 25 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1994376967 EMBASE
TITLE: Inhibitors of glycinamide ribonucleotide formyltransferase as potential cytotoxic agents. Synthesis of 5-deaza-5,6,7,8-tetrahydrohomofolic acid, 5-deaza-5,6,7,8-tetrahydroisohomofolic acid, and 10-formyl-5-deaza-5,6,7,8-tetrahydroisohomofolic acid.
AUTHOR: Taylor, E.C. (correspondence); Yoon, C.; Hamby, J.M.
CORPORATE SOURCE: Department of Chemistry, Princeton University, Princeton, NJ 08544, United States.

SOURCE: Journal of Organic Chemistry, (1994) Vol. 59, No. 23, pp. 7092-7095.
ISSN: 0022-3263 CODEN: JOCEAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jan 1995
Last Updated on STN: 12 Jan 1995

AB Syntheses of three new analogs of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, Lometrexol)-5-deaza-5,6,7,8-tetrahydrohomofolic acid (11), 5-deaza-5,6,7,8-tetrahydroisohomofolic acid (16a), and 10-formyl-5-deaza-5,6,7,8-tetrahydroisohomofolic acid (16b)-are described.

L23 ANSWER 26 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN DUPLICATE 6
ACCESSION NUMBER: 1994376965 EMBASE
TITLE: Asymmetric synthesis of lometrexol ((6R)-5,10-dideaza-5,6,7,8-tetrahydrofolic acid).
AUTHOR: Barnett, C.J. (correspondence); Wilson, T.M.; Wendel, S.R.; Winningham, M.J.; Deeter, J.B.
CORPORATE SOURCE: Chemical Process Res./Developm. Div., Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285-4813, United States.
SOURCE: Journal of Organic Chemistry, (1994) Vol. 59, No. 23, pp. 7038-7045.
ISSN: 0022-3263 CODEN: JOCEAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jan 1995
Last Updated on STN: 12 Jan 1995

AB An enantioselective synthesis of lometrexol (1) which utilizes (5R)-2-piperidone 18 as a key intermediate is described. Lipase-catalyzed enantioselective esterification of 1,3-propanediol derivative 5 provided (R)-(+)-6, the absolute configuration of which was established by X-ray analysis of the (S)-(α-methylbenzyl)carbamate derivative 8. By suitable choice of functional group protection strategies, (R)-(+)-6 could be converted to either enantiomer of azido alcohol 11. The S isomer of 11 was utilized to prepare 18 in three steps. Conversion of 18 to the thiolactam and cyclization with guanidine provided (6R)-5-deaza-5,6,7,8-tetrahydropterin 20. Cyanation of 20 (cuprous cyanide) followed by hydrolysis of the resulting nitrile 21 gave (6R)-5,10-dideaza-5,6,7,8-tetrahydropteroic acid (22). The synthesis of 1 was completed by reaction of 22 with diethyl glutamate via an active ester coupling procedure followed by hydrolysis of the resulting diester.

L23 ANSWER 27 OF 47 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1994300586 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8027993
TITLE: Thienyl and thiazolyl acyclic analogues of 5-deazatetrahydrofolic acid.
AUTHOR: Hodson S J; Bigham E C; Duch D S; Smith G K; Ferone R
CORPORATE SOURCE: Wellcome Research Laboratories, Burroughs Wellcome Company,

Research Triangle Park, North Carolina 27709.
SOURCE: Journal of medicinal chemistry, (1994 Jun 24)
Vol. 37, No. 13, pp. 2112-5.
Journal code: 9716531. ISSN: 0022-2623. L-ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 18 Aug 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 9 Aug 1994

AB Analogues of N-[4-[[3-(2,4-diamino-1,6-dihydro-6-oxo-5-pyrimidinyl)propyl]amino] benzoyl]-L-glutamic acid (5-DACTHF), in which the phenylene group is replaced by either a thienoyl or a thiazolyl group were synthesized. These compounds were prepared by reductive amination of suitably protected pyrimidinylpropionaldehyde with the aminoaroyl glutamates. These glutamates were in turn synthesized from the corresponding nitroaroyl carboxylic acids by condensation with protected glutamic acid followed by catalytic reduction. The compounds were tested as inhibitors of methotrexate uptake as a measure of binding to the reduced folate transport system, as inhibitors of glycinamide ribonucleotide transformylase, as substrates for folylpolyglutamate synthetase, and as inhibitors of tumor cell growth in cell culture. The thiophene analogue was found to be equal in activity to 5-DACTHF in the MCF-7 cell growth inhibition assay while the thiazole analogue was 9-fold more active. Indeed this thiazole was over 4 times more active in the MCF-7 cell line than the clinically investigated compound 5,10-dideaza-5,6,7,8-tetrahydrofolic
acid (DDATHF).

L23 ANSWER 28 OF 47 MEDLINE on STN
ACCESSION NUMBER: 1994076856 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8255099
TITLE: Cross-resistance studies of folylpolyglutamate synthetase-deficient, methotrexate-resistant CCRF-CEM human leukemia sublines.
AUTHOR: McGuire J J; Heitzman K J; Haile W H; Russell C A; McCloskey D E; Piper J R
CORPORATE SOURCE: Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, New York 14263.
CONTRACT NUMBER: CA16056 (United States NCI NIH HHS)
CA25236 (United States NCI NIH HHS)
CA43500 (United States NCI NIH HHS)
SOURCE: Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U.K, (1993 Dec)
Vol. 7, No. 12, pp. 1996-2003.
Journal code: 8704895. ISSN: 0887-6924. L-ISSN: 0887-6924.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 3 Feb 1994
Last Updated on STN: 6 Feb 1998
Entered Medline: 7 Jan 1994

AB CCRF-CEM human leukemia sublines resistant to short-term methotrexate (MTX) exposure as a result of decreased folylpolyglutamate synthetase (FPGS) activity were examined for their response to other cytotoxic agents. The R3/7 and R30dm sublines display 25 and 1%, respectively, of

the FPGS activity of CCRF-CEM cells as measured with MTX in vitro. Response to agents in outgrowth experiments was examined under both continuous exposure (120 h, where MTX resistance is not observed) and short-term (6-14.5 h) exposure. During continuous exposure to various classes of agents, cross-resistance of R3/7 and R30dm that correlated with FPGS level was not observed, although some minor (< or = 3-fold) stochastic variations in sensitivity were noted. These agents included actinomycin D, Adriamycin, etoposide, vincristine, cisplatin, cytosine arabinoside, 5-fluorouracil, and some other antifolates. Cross-resistance during continuous exposure that did correlate with FPGS level was noted, however, to glutamate-containing thymidylate synthase inhibitors (including ICI D1694) and, to a minor extent, to 6-mercaptopurine and 5-fluorodeoxyuridine. Slight collateral sensitivity during continuous exposure that apparently correlated with FPGS level was noted to the lipid-soluble antifolate trimetrexate and to 5,8-dideazapteroyl-L-ornithine, an FPGS-specific inhibitor. In short-term exposures (where MTX resistance of the sublines is observed), the resistant sublines displayed sensitivity or cross-resistance to each agent that was qualitatively similar to that observed for the same agent in continuous exposure. Because of the requirement for reduced folates in the anti-DNA mechanism of action of fluoropyrimidines and the current clinical use of leucovorin (LV) to enhance their effects, the interaction of LV and fluoropyrimidines was examined. The results suggest that even highly FPGS-deficient cells are as sensitive to the effects of LV modulation as are wild-type cells even at fluoropyrimidine exposure times as short as 4 h.

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ACCESSION NUMBER:	1993079995 EMBASE
TITLE:	Isolation and characterization of a human ileocecal carcinoma cell line (HCT-8) subclone resistant to fluorodeoxyuridine.
AUTHOR:	Zhang, Z.-G.; Malmberg, M.; Yin, M.-B.; Slocum, H.K.; Rustum, Y.M., Dr. (correspondence)
CORPORATE SOURCE:	Grace Cancer Drug Center, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, United States.
SOURCE:	Biochemical Pharmacology, (1993) Vol. 45, No. 5, pp. 1157-1164. ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY:	United Kingdom
DOCUMENT TYPE:	Journal; Article
FILE SEGMENT:	016 Cancer 023 Nuclear Medicine 029 Clinical and Experimental Biochemistry 030 Clinical and Experimental Pharmacology 037 Drug Literature Index 048 Gastroenterology
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 25 Apr 1993 Last Updated on STN: 25 Apr 1993

AB A 5-fluoro-2'-deoxyuridine (FdUrd)-resistant subclone (Fd9XR) of HCT-8 (human ileocecal carcinoma) cells was established by two schedules of drug exposure. Initially, cells were exposed to short-term (3 hr) 100 nM FdUrd repeatedly (9 cycles over 8 months), and cells were then exposed to 10 nMFdUrd continuously. During this latter stage, a colony (Fd9XR) with fast growth rate was isolated, expanded, and characterized with respect to mechanisms of resistance to FdUrd and cross-resistance to other chemotherapeutic agents. Fd9XR cells were 1000-fold resistant to FdUrd, but 3-fold more sensitive to 5-fluorouracil (FUra) than HCT-8 cells. After a 3-hr treatment with FdUrd, Fd9XR cells accumulated 6630-, 69-, and

3.7-fold less fluorodeoxyuridylate (FdUMP), fluorouridine triphosphate (FUTP) and acid-insoluble materials, respectively, than HCT-8 cells. However, when FUra was substituted for FdUrd, Fd9XR cells accumulated 9.2-, 3.1-, and 2.3-fold more FdUMP, FUTP and acid-insoluble materials, respectively, than HCT-8 cells. Fd9XR and HCT-8 were similar in their growth rates, combined pools of 5,10-methylenetetrahydrofolates (5,10-CH2H4PteGlu(n)) and tetrahydrofolates (H4PteGlu(n)), thymidine phosphorylase (TP) activity, and level and activity of thymidylate synthase (TS). In contrast, thymidine kinase (TK) activity of Fd9XR was 0.23 and 0.35% of that of HCT-8, for thymidine (dThd) and FdUrd as substrates, respectively. Furthermore, Fd9XR cells exhibited greater sensitivity to the antifolate TS inhibitor ICI D1694 and to methotrexate (MTX) than HCT-8 cells. In addition, dThd alone and in combination with hypoxanthine did not offer any protection against the cytotoxic effect of ICI D1694 in Fd9XR cells. These results indicate that in Fd9XR cells (1) TK deficiency is the primary mechanism of resistance to FdUrd; (2) the greater sensitivity to FUra was associated with higher pools of FdUMP and FUTP with a subsequently higher level of incorporation into cellular RNA; and (3) antifolate compounds, e.g. ICI D1694 and MTX, could be useful agents in the treatment of FdUrd-resistant tumors associated with decreased TK activity and decreased capacity of utilizing dThd.

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ACCESSION NUMBER:	1993019736 EMBASE
TITLE:	5,10-Dideazatetrahydrofolic acid (DDATHF) transport in CCRF-CEM and MA104 cell lines.
AUTHOR:	Pizzorno, G.; Cashmore, A.R.; Moroson, B.A.; Cross, A.D.; Smith, A.K.; Marling- Cason, M.; Kamen, B.A.; Beardsley, G.P. (correspondence)
CORPORATE SOURCE:	Department of Pediatrics, Yale University School of Medicine, New Haven, CT 06510, United States.
SOURCE:	Journal of Biological Chemistry, (1993) Vol. 268, No. 2, pp. 1017-1023. ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article
FILE SEGMENT:	029 Clinical and Experimental Biochemistry 030 Clinical and Experimental Pharmacology 037 Drug Literature Index
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 7 Feb 1993 Last Updated on STN: 7 Feb 1993

AB 5,10-Dideazatetrahydrolic acid (DDATHF) is representative of a new class of antifolates acting through inhibition of de novo purine synthesis. We report here the transport characteristics of the diastereomers of DDATHF, which differ in configuration at C6, and comparison studies with other folate and antifolate analogs. (6R)-DDATHF showed high affinity for the influx system of CCRF-CEM cells with a K(m) of 1.07 μM and an influx V(max) of 4.04 pmol/min/107 cells. Comparative studies with methotrexate yielded an influx K(m) of 4.98 μM and a V(max) of 6.64 pmol/min/107 cells, and with 5- formyltetrahydrofolate an influx K(m) of 2.18 μM and a V(max) of 6.84 pmol/min/107 cells. Uptake of (6R)-DDATHF was competitively inhibited by (6S)-DDATHF, methotrexate (MTX), and 5-formyltetrahydrofolate, all with K(i) values similar to their influx K(m). The (6S)-DDATHF diastereomer had an influx K(m) of 1.04 μM, similar to that of (6R)-DDATHF; however, the V(max) of 1.72 pmol/min/107 cells was 2.3-fold lower than for (6R)-DDATHF. The transport properties of DDATHF were also studied in a mutant cell line (CEM/MTX), resistant to MTX based on impaired drug transport. In this system (6R)-DDATHF showed an influx K(m) of 1.49 μM and a decreased influx V(max) of 0.60

pmol/min/10^7 cells. A similar effect was shown for MTX (K(m) of 7.48 μM, V(max) of 1.02 pmol/min/10^7 cells). The number of binding sites in CCRF-CEM cells was similar for (6R)-DDATHF, (6S)-DDATHF, and MTX, 0.74, 0.71, and 0.76 pmol/10^7 cells, respectively. These values were slightly higher in the CEM/MTX cell line (1.07 and 1.09 pmol/10^7 cells for (6R)-DDATHF and MTX, respectively). Treatment of CCRF-CEM cells with either the N- hydroxysuccinimide ester of MTX or the corresponding N-hydroxysuccinimide ester of (6R)-DDATHF caused substantial inhibition (>90%) of the influx of (6R)-[3H]DDATHF and [3H]MTX, respectively. These results suggest strongly that DDATHF and MTX share a common influx mechanism through the reduced folate transport system. The internalization of DDATHF by monkey kidney epithelial MA104 cells, which express a high affinity folate receptor, was also studied. Competitive binding studies using purified folate receptor and radiolabeled 5-methyltetrahydrofolate showed that (6S)- and (6R)-DDATHF both had I50 values lower than 5-methyltetrahydrofolate (12 nM). Further studies indicate that both DDATHF isomers are actively intracellularly concentrated through this route and are also rapidly converted to high chain length polyglutamates. Transport via this system was inhibited in folate-depleted cells by 10 nM folic acid. At a concentration of 10 nM, receptor-mediated uptake results in greater drug accumulation in receptor-positive cells compared to receptor-negative cells.

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ACCESSION NUMBER: 1993223807 EMBASE
TITLE: Cancer drug development: Current research and patents- 1992 - part 1.
AUTHOR: Bair, K.W. (correspondence)
CORPORATE SOURCE: Sandoz Research Institute, Oncology Research, 59 Route 10, East Hanover, NJ 07936-1080, United States.
SOURCE: Current Opinion in Therapeutic Patents, (1993) Vol. 3, No. 6, pp. 695-742. ISSN: 0962-2594 CODEN: COTPES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Aug 1993
Last Updated on STN: 29 Aug 1993

L23 ANSWER 32 OF 47 MEDLINE on STN DUPLICATE 8

ACCESSION NUMBER: 1992203248 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1552503
TITLE: Synthesis and biological activity of acyclic analogues of 5,10-dideaza-5,6,7,8 -tetrahydrofolic acid.
AUTHOR: Shih C; Gossett L S; Worzalla J F; Rinzel S M; Grindey G B; Harrington P M; Taylor E C
CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly & Company, Indianapolis, Indiana 46285.
SOURCE: Journal of medicinal chemistry, (1992 Mar 20) Vol. 35, No. 6, pp. 1109-16. Journal code: 9716531. ISSN: 0022-2623. L-ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 9 May 1992
Last Updated on STN: 9 May 1992
Entered Medline: 28 Apr 1992

AB The synthesis and biological evaluation of a number of analogues of N-[4-[4-(2,4-diamino-1,6-dihydro-6-oxo-5-pyrimidyl) butyl]benzoyl]-L-glutamic acid (2) (7-DM-DDATHF), an acyclic modification of the novel folate antimetabolite 5,10-dideazatetrahydrofolic acid (DDATHF), are described. The synthetic procedure utilized previously for the synthesis of 2, 15, and 16 was extended to the preparation of analogues modified in the benzoyl region with thiophene and methylene groups replacing the benzene ring (compounds 27a-c) and in the glutamate region with aspartic acid and phenylalanine replacing L-glutamic acid (compounds 36, 37). The 2-amino-4,6-dioxo derivative 33 was obtained from intermediate 30 via a palladium-catalyzed carbon-carbon coupling reaction with diethyl (4-iodobenzoyl)-L-glutamate, followed by reduction and removal of protecting groups with base. Cell culture cytotoxicity studies of all of the above acyclic analogues of DDATHF against CCRF-CEM human lymphoblastic leukemic cells gave IC50s ranging from 0.042 greater than 48 microM. Inhibition and cell culture reversal studies against isolated enzymes suggest the mode of action of these compounds. Compound 2 was only 3-fold less inhibitory toward glycinamide ribonucleotide formyltransferase (GARFT, isolated from L1210 leukemic cells) than DDATHF itself. These acyclic analogues were less efficient substrates for the enzyme folylpolyglutamate synthetase (FPGS) compared with their bicyclic counterparts. Moderate antitumor activity was observed for compound 2 against 6C3HED lymphosarcoma and C3H mammary adenocarcinoma in vivo.

L23 ANSWER 33 OF 47 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 1992363967 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1500451
TITLE: Bioanalysis of the investigational anti-tumour drug 5,10-dideaza-5,6,7,8 -tetrahydrofolic acid by high-performance liquid chromatography with ultraviolet detection.
AUTHOR: van Tellingen O; Sips J H; Beijnen J H; Schornagel J H; Nooyen W J
CORPORATE SOURCE: Department of Clinical Chemistry, Netherlands Cancer Institute, Amsterdam.
SOURCE: Journal of chromatography, (1992 Apr 15) Vol. 576, No. 1, pp. 158-62.
Journal code: 0427043. ISSN: 0021-9673. L-ISSN: 0021-9673.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 25 Sep 1992
Last Updated on STN: 25 Sep 1992
Entered Medline: 17 Sep 1992

AB A high-performance liquid chromatographic (HPLC) method with ultraviolet detection at 278 nm is presented for the determination of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid in plasma. Sample pretreatment was achieved by using cation-exchange solid-phase extraction columns with methotrexate as internal standard. Chromatographic separation was based on ion-pair HPLC with 1-octanesulphonic acid as the ion-pairing compound. The detection limit was 10 ng/ml using an 500-microliters sample volume. The assay was linear from the detection limit up to 5000 ng/ml with good reproducibility. The applicability of the assay was demonstrated in a study in the rat.

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ACCESSION NUMBER: 1992025608 EMBASE
TITLE: Synthesis of 10-substituted 'open-chain' analogues of 5,10-dideaza-5,6,7,8 -tetrahydrofolic acid (DDATHF, lometrexol).
AUTHOR: Taylor, E.C.; Schrader, T.H.; Walensky, L.D.
CORPORATE SOURCE: Department of Chemistry, Princeton University, Princeton, NJ 08544, United States.
SOURCE: Tetrahedron, (1992) Vol. 48, No. 1, pp. 19-32. ISSN: 0040-4020 CODEN: TETRAB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Mar 1992
Last Updated on STN: 20 Mar 1992

AB Several novel and very potent folate antimetabolite, structurally based upon our previously described 'open-chain' version of DDATHF but carrying 1-carbon substituents in the 10-position, have been synthesized. A key synthetic sequence involving a palladium-catalyzed C-C coupling reaction, oxymercuration, and Wittig olefination constitutes a new route to α-branched 4-styrene carboxylic acids. Classical construction of the pyrimidine ring from the key intermediate 6 followed by glutamate coupling furnished 12, which upon hydrolysis furnished the 10-methenyl derivative 13. The 10-methenyl functionality in 12 was further modified to afford the 10-methyl-, 10-hydroxymethyl- and 10-dihydroxyboromethyl derivatives 22, 3 and 25 respectively; double bond isomerization led to the 10-methyl-9,10-didehydro analog 20. Preliminary in vitro cell culture screening showed that many of these 'open-chain' analogs rivaled DDATHF itself as cytotoxic agents, and were about ten times more active than the parent 'open-chain' DDATHF analog lacking a C-10 substituent. Surprisingly, however, compounds 13 and 22 were inactive in vivo.

L23 ANSWER 35 OF 47 MEDLINE on STN DUPLICATE 11

ACCESSION NUMBER: 1991199071 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1707749
TITLE: (6R)-5,10-Dideaza-5,6,7, 8-tetrahydrofolic acid effects on nucleotide metabolism in CCRF-CEM human T-lymphoblast leukemia cells.
AUTHOR: Pizzorno G; Moroson B A; Cashmore A R; Beardsley G P
CORPORATE SOURCE: Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut 06510.
CONTRACT NUMBER: CA 42367 (United States NCI NIH HHS)
CA 57320 (United States NCI NIH HHS)
SOURCE: Cancer research, (1991 May 1) Vol. 51, No. 9, pp. 2291-5.
Journal code: 2984705R. ISSN: 0008-5472. L-ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199105
ENTRY DATE: Entered STN: 7 Jun 1991
Last Updated on STN: 6 Feb 1998

Entered Medline: 17 May 1991

AB (6R)-5,10-Dideaza-5,6,7,8-tetrahydrofolic acid [(6R)DDATHF] is a folate antimetabolite with activity specifically directed against de novo purine synthesis, primarily through inhibition of glycinamide ribonucleotide transformylase. This inhibition resulted in major changes in the size of the nucleotide pools in CCRF-CEM cells. After a 4-h incubation with 1 microM (6R)DDATHF, dramatic reductions in the ATP and GTP pools were observed, with almost no effect on CTP, UTP, and deoxyribonucleotide pools. When the incubation was continued in drug-free medium, recovery of ATP and GTP pools was protracted. ATP did not return to normal until 24-36 h, and GTP pools were only partially repleted by 48 h. The ATP and GTP pools were not affected when the initial 4-h incubation with (6R)DDATHF was conducted in the presence of 100 microM hypoxanthine. Addition of hypoxanthine to the medium after a 4-h incubation with (6R)DDATHF caused rapid recovery of the ATP and GTP pools. Similar effects were seen when the purine precursor aminoimidazole carboxamide was used in place of hypoxanthine. The effect of (6R)DDATHF on nucleotide pools and the capability of hypoxanthine or aminoimidazole carboxamide to prevent or reverse this phenomenon correlated directly with the inhibition of cell growth. Presumably as a consequence of the decrease in purine nucleotide triphosphate levels, the conversion of exogenously added uridine, thymidine, and deoxyuridine to nucleotides was markedly decreased. These effects were protracted for almost 48 h and were also reversed by hypoxanthine. Differential repletion of ATP and GTP pools after (6R)DDATHF pre-treatment demonstrated that diminished precursor phosphorylation is primarily a consequence of GTP rather than ATP starvation.

L23 ANSWER 36 OF 47 MEDLINE on STN DUPLICATE 12

ACCESSION NUMBER:	1991140586 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 1995883
TITLE:	Synthesis and biological evaluation of 5-deazaisofolic acid, 5-deaza-5,6,7,8-tetrahydroisofolic acid, and their N9-substituted analogues.
AUTHOR:	Singh S K; Dev I K; Duch D S; Ferone R; Smith G K; Freisheim J H; Hynes J B
CORPORATE SOURCE:	Department of Pharmaceutical Sciences, Medical University of South Carolina, Charleston 29425.
SOURCE:	Journal of medicinal chemistry, (1991 Feb) Vol. 34, No. 2, pp. 606-10. Journal code: 9716531. ISSN: 0022-2623. L-ISSN: 0022-2623.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	199103
ENTRY DATE:	Entered STN: 12 Apr 1991 Last Updated on STN: 6 Feb 1998 Entered Medline: 27 Mar 1991

AB Prompted by recent disclosures concerning the potent antitumor activities of 5-deaza-5,6,7,8-tetrahydrofolic acid and 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF), we have prepared 5-deazaisofolic acid (3a) and 5-deaza-5,6,7,8-tetrahydroisofolic acid (4a). Reductive condensation of 2,6-diamino-3,4-dihydro-4- oxopyrido[2,3-d]pyrimidine with di-tert-butyl N-(4-formylbenzoyl)-L-glutamate and subsequent deprotection with trifluoroacetic acid yielded 5-deazaisofolic acid in good yield. Catalytic hydrogenation of this analogue then gave 4a. The 9-CH3 and 9-CHO modifications of 3a and the 9-CH3 derivative of 4a were also

synthesized. Each of the new analogues was evaluated with a variety of folate-requiring enzymes as well as MCF-7 cells in culture. Compound 4a had an IC50 of ca. 1 microM against MCF-7 cells and was nearly 100-fold less potent than DDATHF in this regard. The three oxidized isofolate analogues were all poor inhibitors of tumor cell growth.

L23 ANSWER 37 OF 47 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 1991129993 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1993335
TITLE: Competitive particle concentration fluorescence immunoassay for measuring 5,10-dideaza-5,6, 7,8-tetrahydrofolic acid (lometrexol) in serum.
AUTHOR: Taber L D; O'Brien P; Bowsher R R; Sportsman J R
CORPORATE SOURCE: Department of Biochemistry Research, Lilly Corporate Center, Indianapolis, IN 46285.
SOURCE: Clinical chemistry, (1991 Feb) Vol. 37, No. 2, pp. 254-60.
Journal code: 9421549. ISSN: 0009-9147. L-ISSN: 0009-9147.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 5 Apr 1991
Last Updated on STN: 5 Apr 1991
Entered Medline: 21 Mar 1991

AB A competitive particle concentration fluorescence immunoassay (PCFIA) is described for measuring 5,10-dideaza-5,6,7, 8-tetrahydrofolic acid (lometrexol; Lilly) in human serum. b-Phycoerythrin-labeled lometrexol competes with free lometrexol for binding to a limiting concentration of lometrexol-specific antibodies immobilized by a second antibody to submicrometer-diameter polystyrene particles in specially designed 96-well plates. Reaction particles are washed and concentrated onto filter membranes in the wells of the plates and the fluorescence is measured at 575 nm. The method, including sample preparation and data reduction, is automated and can be completed in less than 2 h. The assay has a standard curve maximum measurable concentration of 1000 micrograms/L and a minimum detectable concentration of 0.1 microgram/L. Analytical recovery of lometrexol in serum is quantitative at concentrations greater than 1 micrograms/L. Intra- and interassay coefficients of variation at 50 micrograms/L in serum are 7.1% (n = 9) and 7.5% (n = 33), respectively. The cross-reactivity of naturally occurring folates, folic acid analogs, and the anti-cancer agent methotrexate is minimal. We report the use of the PCFIA during Phase I clinical studies designed to evaluate the pharmacokinetics of lomextrexol after intravenous administration to cancer patients.

L23 ANSWER 38 OF 47 EMBASE
ACCESSION NUMBER: 1990198213 EMBASE
TITLE: A convergent synthesis of 5,10-dideaza-5, 6,7,8-tetrahydrofolic acid and 5,10-dideaza-5,6,7,8-tetrahydrohomofolic acid. An effective principle for carbonyl group activation.
AUTHOR: Taylor, E.C.; Harrington, P.M.
CORPORATE SOURCE: Department of Chemistry, Princeton University, Princeton, NJ 08544, United States.
SOURCE: Journal of Organic Chemistry, (1990) Vol. 55, No. 10, pp. 3222-3227.
ISSN: 0022-3263 CODEN: JOCEAH

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Dec 1991
Last Updated on STN: 13 Dec 1991

L23 ANSWER 39 OF 47 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 1991179635 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2080047
TITLE: 5,10-Dideaza-5,6,7,8
-tetrahydrofolic acid (DDATHF): a
potent inhibitor of purine biosynthesis.
AUTHOR: Anonymous
SOURCE: Nutrition reviews, (1990 Nov) Vol. 48, No. 11,
pp. 421-3. Ref: 4
Journal code: 0376405. ISSN: 0029-6643. L-ISSN: 0029-6643.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199105
ENTRY DATE: Entered STN: 19 May 1991
Last Updated on STN: 3 Feb 1997
Entered Medline: 1 May 1991

L23 ANSWER 40 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1989280254 EMBASE
TITLE: Asymmetric synthesis and absolute configuration of
5,10-dideaza-5,6,7,8-tetrahydropteroic acid and
5,10-dideaza-5,6,7,8
-tetrahydrofolic acid (DDATHF).
AUTHOR: Barnett, C.J.; Wilson, T.M.
CORPORATE SOURCE: Chemical Process Research and Development Division, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, United States.
SOURCE: Tetrahedron Letters, (1989) Vol. 30, No. 46, pp.
6291-6294.
ISSN: 0040-4039 CODEN: TELEAY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1991
Last Updated on STN: 12 Dec 1991
AB Lipase-catalyzed enantioselective esterification of 2-substituted 1,3-diols has been utilized in the asymmetry synthesis and consequent configurational assignments of the title compounds.

L23 ANSWER 41 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1989204498 EMBASE
TITLE: Convergent and efficient palladium-effected synthesis of
5,10-dideaza-5,6,7,8
-tetrahydrofolic acid (DDATHF).
AUTHOR: Taylor, E.C.; Wong, G.S.K.
CORPORATE SOURCE: Department of Chemistry, Princeton University, Princeton, NJ 08544, United States.
SOURCE: Journal of Organic Chemistry, (1989) Vol. 54, No.

15, pp. 3618-3624.
ISSN: 0022-3263 CODEN: JOCEAH
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1991
Last Updated on STN: 12 Dec 1991

L23 ANSWER 42 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1989205400 EMBASE
TITLE: Synthesis and antitumor activity of 5-deaza-5, 6,7,8-tetrahydrofolic acid and its N10-substituted analogues.
AUTHOR: Taylor, E.C.; Hamby, J.M.; Shih, C.; Grindey, G.B.; Rinzel, S.M.; Beardsley, G.P.; Moran, R.G.
CORPORATE SOURCE: Department of Chemistry, Princeton University, Princeton, NJ 08544, United States.
SOURCE: Journal of Medicinal Chemistry, (1989) Vol. 32, No. 7, pp. 1517-1522.
ISSN: 0022-2623 CODEN: JMCMAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1991
Last Updated on STN: 12 Dec 1991
AB Syntheses of 5-deaza-5,6,7,8-tetrahydrofolic acid (7a) and its 10-formyl (7b), 10-acetyl (7c), and 10-methyl (7d) derivatives are described. These compounds, prepared as analogues of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF), the lead compound of a new class of folate antimetabolites, exhibit potent growth inhibition against leukemic cells in culture as well as substantial antitumor activity against transplantable murine solid tumors in vivo.

L23 ANSWER 43 OF 47 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 1990090888 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2598407
TITLE: Synergy between 5,10-dideaza-5,6,7,8-tetrahydrofolic acid and methotrexate in mice bearing L1210 tumors.
AUTHOR: Ferguson K; Boschelli D; Hoffman P; Oronsky A; Whiteley J; Webber S; Galivan J; Freishiem J; Hynes J; Kerwar S S
CORPORATE SOURCE: Medical Research Division, American Cyanamid Company, Pearl River, NY 10965.
CONTRACT NUMBER: CA 25014 (United States NCI NIH HHS)
CA 25933 (United States NCI NIH HHS)
CA 41461 (United States NCI NIH HHS)
+
SOURCE: Cancer chemotherapy and pharmacology, (1989) Vol. 25, No. 3, pp. 173-6.
Journal code: 7806519. ISSN: 0344-5704. L-ISSN: 0344-5704.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199001
ENTRY DATE: Entered STN: 28 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 26 Jan 1990

AB In vivo studies with 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF), an inhibitor of glycinamide ribonucleotide transformylase, indicate that at doses ranging from 2.5 to 10 mg/kg, it prolongs the survival of mice implanted with L1210 tumors. Lower doses of this agent have no effect. Parallel studies with methotrexate indicate that DDATHF is not as potent or as efficacious as methotrexate in this animal model. Low doses of DDATHF combined with low doses of methotrexate can cause a significant increase in the survival of L1210 tumor-bearing mice, suggesting synergism between these two antifolates.

L23 ANSWER 44 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1989006321 EMBASE
TITLE: Analogs of tetrahydrofolate directed at folate-dependent purine biosynthetic enzymes. Characteristics of mediated entry and transport-related resistance in L1210 cells for 5,10-dideazatetrahydrofolate and two 10-alkyl derivatives.
AUTHOR: Sirotnak, F.M.; Otter, G.M.; Piper, J.R.; DeGraw, J.I.
CORPORATE SOURCE: Laboratory for Molecular Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, United States.
SOURCE: Biochemical Pharmacology, (1988) Vol. 37, No. 24, pp. 4775-4777.
ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
023 Nuclear Medicine
025 Hematology
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1991
Last Updated on STN: 12 Dec 1991

AB A cytotoxic analog of tetrahydrofolate, 5-10-dideazatetrahydrofolate (DDTHF), was synthesized recently and found [8-11] to have significant antitumor activity in animal models naturally refractive to methotrexate. Additional studies with this analog suggest [8-11] that is cytotoxic activity is associated with effects on purine biosynthesis. Our own interest in these structures centers upon the issues of their membrane transport and transport-related acquired resistance in tumor cells which form the basis of this report.

L23 ANSWER 45 OF 47 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 1989037080 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3184124
TITLE: Synthesis and antifolate activity of 5-methyl-5,10-dideaza analogues of aminopterin and folic acid and an alternative synthesis of 5,10-dideazatetrahydrofolic acid, a potent inhibitor of glycinamide ribonucleotide formyltransferase.
AUTHOR: Piper J R; McCaleb G S; Montgomery J A; Kisliuk R L; Gaumont Y; Thorndike J; Sirotnak F M
CORPORATE SOURCE: Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35255.

CONTRACT NUMBER: CA18856 (United States NCI NIH HHS)
CA22764 (United States NCI NIH HHS)
CA25236 (United States NCI NIH HHS)
+
SOURCE: Journal of medicinal chemistry, (1988 Nov) Vol. 31, No. 11, pp. 2164-9.
Journal code: 9716531. ISSN: 0022-2623. L-ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198812
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 5 Dec 1988

AB The title compounds were prepared in extensions of a general synthetic approach used earlier to prepare 5-alkyl-5-deaza analogues of classical antifolates. Wittig condensation of 2,4-diaminopyrido[2,3-d]pyrimidine-6-carboxaldehyde (2a) and its 5-methyl analogue 2b with [4-(methoxycarbonyl)benzylidene] triphenylphosphorane gave 9,10-ethenyl precursors 3a and 3b. Hydrogenation (DMF, ambient, 5% Pd/C) of the 9,10-ethenyl group of 3b followed by ester hydrolysis led to 4-[2-(2,4-diamino-5-methylpyrido[2,3-d]pyrimidin-6-yl)ethyl]ben zoi c acid (5), which was converted to 5-methyl-5,10-dideazaaminopterin (6) via coupling with dimethyl L-glutamate (mixed-anhydride method using i-BuOCOCl) followed by ester hydrolysis. Standard hydrolytic deamination of 6 gave 5-methyl-5,10-dideazafolic acid (7). Intermediates 3a and 3b were converted through concomitant deamination and ester hydrolysis to 8a and 8b. Peptide coupling of 8a,b (using (EtO)2POCN) with diesters of L-glutamic acid gave intermediate esters 9a and 9b. Hydrogenation of both the 9,10 double bond and the pyrido ring of 9a and 9b (MeOH-0.1 N HCl, 3.5 atm, Pt) was followed by ester hydrolysis to give 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (11a) and the 5-methyl analogue 11b. Biological evaluation of 6, 7, 11a, and 11b for inhibition of dihydrofolate reductase (DHFR) isolated from L1210 cells and for growth inhibition and transport characteristics toward L1210 cells revealed 6 to be less potent than methotrexate in the inhibition of DHFR and cell growth. Compounds 6, 11a, and 11b were transported into cells more efficiently than methotrexate. Growth inhibition IC50 values for 11a and 11b were 57 and 490 nM, respectively; the value for 11a is in good agreement with that previously reported (20-50 nM). In tests against other folate-utilizing enzymes, 11a and 11b were found to be inhibitors of glycinamide ribonucleotide formyltransferase (GAR formyltransferase) from one bacterial (Lactobacillus casei) and two mammalian (Manca and L1210) sources with 11a being decidedly more inhibitory than 11b. Neither 11a nor 11b inhibited aminoimidazolecarboxamide ribonucleotide formyltransferase. These results support reported evidence that 11a owes its observed antitumor activity to interference with the purine de novo pathway with the site of action being GAR formyltransferase.

L23 ANSWER 46 OF 47 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 1988325440 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3166364
TITLE: Synthesis and biological properties of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid.
AUTHOR: Boschelli D H; Webber S; Whiteley J M; Oronsky A L; Kerwar S S
CORPORATE SOURCE: Department of Chemistry, Lederle Laboratories, Pearl River,

New York 10965.
CONTRACT NUMBER: CA 11778 (United States NCI NIH HHS)
CA 38849 (United States NCI NIH HHS)
GM 22125 (United States NIGMS NIH HHS)
SOURCE: Archives of biochemistry and biophysics, (1988 Aug 15) Vol. 265, No. 1, pp. 43-9.
Journal code: 0372430. ISSN: 0003-9861. L-ISSN: 0003-9861.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198809
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 28 Sep 1988

AB The synthesis of the antifolate 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF) has been modified. It is prepared from 2-acetamido-6-formyl-4(3H)-pyrido[2,3-b]pyrimidone and [P-(N-[1,3-bis(ethoxycarbonyl)propan-1-yl]aminocarbonyl)] phenylmethyl]-triphenylphosphonium bromide. The synthesis proceeds via a sodium hydride promoted Wittig condensation in 1-methyl-2-pyrrolidone followed by catalytic reduction, mild base hydrolysis, and acid precipitation of the product. Synthesis of DDATHF is achieved in a total of seven steps from commercially available reagents. DDATHF is transported effectively into CCRF-CEM cells and inhibits growth of both human (CEM) and murine (L1210) cells in culture. Studies reported here support the view that methotrexate and DDATHF are transported via a shared transport mechanism.

L23 ANSWER 47 OF 47 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1985152925 EMBASE
TITLE: 5,10-Dideaza-5,6,7,8-tetrahydrofolic acid (DATHF), a potent antifolate inhibitory to de novo purine synthesis.
AUTHOR: Moran, R.G.; Taylor, E.C.; Beardsley, G.P.
CORPORATE SOURCE: Children's Hospital of Los Angeles, Los Angeles, CA, United States.
SOURCE: Proceedings of the American Association for Cancer Research, (1985) Vol. VOL. 26, pp. No. 910.
CODEN: PAACA3
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 016 Cancer
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991

=> d his

(FILE 'HOME' ENTERED AT 13:07:18 ON 29 JAN 2010)

FILE 'REGISTRY' ENTERED AT 13:08:22 ON 29 JAN 2010
L1 3075 S TETRAHYDROFOLATE
L2 0 S TETRAHYDROFOLATE/CN
E "TETRAHYDROFOLATE"/CN 25
E "TETRAHYDROFOLIC ACID"/CN 25
L3 1 S E3
E "TETRAHYDROFOLIC ACID"/CN 25

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                E "METHYL-TETRAHYDROFOLATE"/CN 25
                E "5-METHYLTETRAHYDROFOLATE"/CN 25
                E "5-MTHF"/CN 25
                E "5,10-METHYLENETETRA"/CN 25
                E "5,10-METHYLENETETRAHYDROFOLATE"/CN 25
                E "MTHF"/CN 25
L4            1 S E3

     FILE 'CAPLUS' ENTERED AT 13:13:16 ON 29 JAN 2010
L5         1971 S L3 OR METHYLENE-TETRAHYDROFOLATE OR METHYL-TETRAHYDROFOLATE
L6            8 S L5 AND (PEMETREXED OR RALITREXED OR LOMETREXOL)
L7            8 DUP REM L6 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 13:15:04 ON 29 JAN 2010
                E "METHYLENETETRAHYDROFOLATE"/CN 25
L8            8 S PEMETREXED
L9            0 S RALITREXED
L10           1 S RALTITREXED
L11           2 S LOMETREXOL

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:16:34 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:16:40 ON 29 JAN 2010
                SET SMARTSELECT ON
L12          SEL L3 1- CHEM :      12 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:16:41 ON 29 JAN 2010
L13         2719 S L12

     FILE 'REGISTRY' ENTERED AT 13:17:07 ON 29 JAN 2010
                SET SMARTSELECT ON
L14          SEL L8 1- CHEM :      24 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:09 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
                SET SMARTSELECT ON
L15          SEL L10 1- CHEM :       7 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:10 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
                SET SMARTSELECT ON
L16          SEL L11 1- CHEM :       6 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:11 ON 29 JAN 2010
L17         3520 S L14
L18         5017 S L15
L19          419 S L16
L20         8299 S L17 OR L18 OR L19
L21           69 S L13 AND L20
L22           66 S L21 AND PD<20041222
L23           47 DUP REM L22 (19 DUPLICATES REMOVED)

=> d 13
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y
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L3   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2010 ACS on STN
RN   135-16-0  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   L-Glutamic acid, N-[4-[[(2-amino-3,4,5,6,7,8-hexahydro-4-oxo-6-
     pteridinyl)methyl]amino]benzoyl]-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Glutamic acid, N-[p-[[(2-amino-3,4,5,6,7,8-hexahydro-4-oxo-6-
     pteridinyl)methyl]amino]benzoyl]-, L-  (7CI, 8CI)
CN   L-Glutamic acid, N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-
     pteridinyl)methyl]amino]benzoyl]-  (9CI)
OTHER NAMES:
CN   (-)-L-5,6,7,8-Tetrahydrofolic acid
CN   5,6,7,8-Tetrahydrofolic acid
CN   L-5,6,7,8-Tetrahydrofolic acid
CN   Tetrahydrofolic acid
CN   Tetrahydropteroylglutamic acid
CN   THFA
FS   STEREOSEARCH
DR   60201-89-0, 18632-03-6, 14231-42-6, 15582-27-1, 4172-42-3
MF   C19 H23 N7 O6
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO,
       CA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU,
       EMBASE, IPA, MSDS-OHS, PIRA, PROMT, RTECS*, TOXCENTER, USPAT2,
       USPATFULL, USPATOLD, VETU
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**
         (**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.
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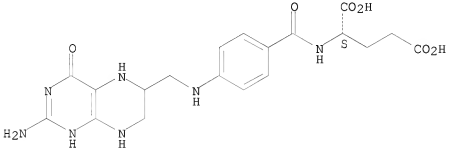

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

           1251 REFERENCES IN FILE CA (1907 TO DATE)
             95 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
           1253 REFERENCES IN FILE CAPLUS (1907 TO DATE)


=> d his

     (FILE 'HOME' ENTERED AT 13:07:18 ON 29 JAN 2010)

     FILE 'REGISTRY' ENTERED AT 13:08:22 ON 29 JAN 2010
L1         3075 S TETRAHYDROFOLATE
```

```
L2            0 S TETRAHYDROFOLATE/CN
                E "TETRAHYDROFOLATE"/CN 25
                E "TETRAHYDROFOLIC ACID"/CN 25
L3            1 S E3
                E "TETRAHYDROFOLIC ACID"/CN 25
                E "METHYL-TETRAHYDROFOLATE"/CN 25
                E "5-METHYLTETRAHYDROFOLATE"/CN 25
                E "5-MTHF"/CN 25
                E "5,10-METHYLENETETRA"/CN 25
                E "5,10-METHYLENETETRAHYDROFOLATE"/CN 25
                E "MTHF"/CN 25
L4            1 S E3

     FILE 'CAPLUS' ENTERED AT 13:13:16 ON 29 JAN 2010
L5         1971 S L3 OR METHYLENE-TETRAHYDROFOLATE OR METHYL-TETRAHYDROFOLATE
L6            8 S L5 AND (PEMETREXED OR RALITREXED OR LOMETREXOL)
L7            8 DUP REM L6 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 13:15:04 ON 29 JAN 2010
                E "METHYLENETETRAHYDROFOLATE"/CN 25
L8            8 S PEMETREXED
L9            0 S RALITREXED
L10           1 S RALTITREXED
L11           2 S LOMETREXOL

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:16:34 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:16:40 ON 29 JAN 2010
                SET SMARTSELECT ON
L12          SEL L3 1- CHEM :      12 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:16:41 ON 29 JAN 2010
L13        2719 S L12

     FILE 'REGISTRY' ENTERED AT 13:17:07 ON 29 JAN 2010
                SET SMARTSELECT ON
L14          SEL L8 1- CHEM :      24 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:09 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
                SET SMARTSELECT ON
L15          SEL L10 1- CHEM :       7 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:10 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
                SET SMARTSELECT ON
L16          SEL L11 1- CHEM :       6 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:11 ON 29 JAN 2010
L17        3520 S L14
L18        5017 S L15
L19         419 S L16
L20        8299 S L17 OR L18 OR L19
L21          69 S L13 AND L20
L22          66 S L21 AND PD<20041222
L23          47 DUP REM L22 (19 DUPLICATES REMOVED)
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FILE 'REGISTRY' ENTERED AT 13:19:22 ON 29 JAN 2010

FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:19:22 ON 29 JAN 2010

=> FIL REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	9.99	323.69

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-6.80

FILE 'REGISTRY' ENTERED AT 13:24:28 ON 29 JAN 2010
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DICTIONARY FILE UPDATES: 27 JAN 2010 HIGHEST RN 1203797-79-8

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predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> E "5-METHYLTETRAHYDROFOLIC ACID"/CN 25
E1 1 5-METHYLTETRAHYDROFOLATE:HOMOCYSTEINE S-METHYLTRANSFERASE (STREPTOMYCES CLAVULIGERUS STRAIN ATCC27064 GENE METH)/CN
E2 1 5-METHYLTETRAHYDROFOLATE:NAD OXIDOREDUCTASE/CN
E3 1 --> 5-METHYLTETRAHYDROFOLIC ACID/CN
E4 1 5-METHYLTETRAHYDROFOLIC ACID SODIUM SALT/CN
E5 1 5-METHYLTETRAHYDROFOLIC ACID-9,3',5'-3H/CN
E6 1 5-METHYLTETRAHYDROFURAN-2-ETHANOL/CN
E7 1 5-METHYLTETRAHYDROFURFURYL ALCOHOL/CN
E8 1 5-METHYLTETRAHYDROFUROIC ACID/CN
E9 1 5-METHYLTETRAHYDROHOMOFOLIC ACID/CN
E10 1 5-METHYLTETRAHYDROISOBENZOFURAN-1,3-DIONE/CN
E11 1 5-METHYLTETRAHYDROPHTHALIC ANHYDRIDE/CN
E12 1 5-METHYLTETRAHYDROPTERIN/CN
E13 1 5-METHYLTETRAHYDROPTEROYL HEPTAGLUTAMATE/CN
E14 1 5-METHYLTETRAHYDROPTEROYL HEXAGLUTAMATE/CN
E15 1 5-METHYLTETRAHYDROPTEROYL MONOGLUTAMATE/CN
E16 1 5-METHYLTETRAHYDROPTEROYL TETRAGLUTAMATE/CN
E17 1 5-METHYLTETRAHYDROPTEROYL TRIGLUTAMATE-HOMOCYSTEINE METHYLTRANSFERASE (SACCHAROMYCES CEREVISIAE STRAIN S288C GENE MET6)/CN
E18 1 5-METHYLTETRAHYDROPTEROYL-A-GLUTAMYLGLUTAMIC ACID/CN
E19 1 5-METHYLTETRAHYDROPTEROYL-Γ-GLUTAMYL-Γ-GLUTAMYLGLUTAMIC ACID/CN
E20 1 5-METHYLTETRAHYDROPTEROYL-Γ-HEPTAGLUTAMATE/CN

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E21          1     5-METHYLTETRAHYDROPTEROYLDIGLUTAMIC ACID/CN
E22          1     5-METHYLTETRAHYDROPTEROYLGLUTAMIC ACID/CN
E23          1     5-METHYLTETRAHYDROPTEROYLPENTAGLUTAMATE/CN
E24          1     5-METHYLTETRAHYDROPTEROYLTRIGLUTAM ATE--HOMOCYSTEINE
METHYLTRANSFERASE PROTEIN (RALSTONIA SOLANACEARUM STRAIN GMI1000 GENE METE)/CN
E25          1     5-METHYLTETRAHYDROPTEROYLTRIGLUTAMATE HOMOCYSTEINE
METHYLTRANSFERASE/CN

=> S E3
L24          1 "5-METHYLTETRAHYDROFOLIC ACID"/CN

=> DIS L24 1 SQIDE

L24  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2010 ACS on STN
RN   134-35-0  REGISTRY
CN   L-Glutamic acid, N-[4-[[(2-amino-3,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6-
     pteridinyl)methyl]amino]benzoyl]-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Glutamic acid, N-[p-[[(2-amino-5,6,7,8-tetrahydro-4-hydroxy-5-methyl-6-
     pteridinyl)methyl]amino]benzoyl]-, L- (8CI)
CN   Glutamic acid, N-[p-[[(2-amino-5,6,7,8-tetrahydro-4-hydroxy-5-methyl-6-
     pteridinyl)methyl]amino]benzoyl]- (6CI)
CN   L-Glutamic acid, N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6-
     pteridinyl)methyl]amino]benzoyl]- (9CI)
OTHER NAMES:
CN   5-Methyl-5,6,7,8-tetrahydrofolic acid
CN   5-Methyl-5,6,7,8-tetrahydropteroyl-L-glutamic acid
CN   5-Methyltetrahydrofolic acid
CN   5-Methyltetrahydropteroyl monoglutamate
CN   5-Methyltetrahydropteroylglutamic acid
CN   N-Methyltetrahydrofolate
CN   N-Methyltetrahydrofolic acid
CN   N5-Methyltetrahydrofolate
CN   N5-Methyltetrahydrofolic acid
CN   N5-Methyltetrahydropteroylglutamate
CN   Prefolic A
FS   STEREOSEARCH
DR   3922-58-5, 76937-22-9
MF   C20 H25 N7 O6
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO,
       CA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, DDFU, DRUGU, EMBASE, IPA,
       MEDLINE, PROMT, PROUSDDR, TOXCENTER, USPAT2, USPATFULL, VETU
         (*File contains numerically searchable property data)
DT.CA  CAplus document type:  Conference; Dissertation; Journal; Patent; Report
RL.P   Roles from patents:  ANST (Analytical study); BIOL (Biological study);
       PREP (Preparation); PROC (Process); PRPH (Prophetic); RACT (Reactant or
       reagent); USES (Uses); NORL (No role in record)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); PREP (Preparation); PRP (Properties); USES (Uses)
RL.NP  Roles from non-patents:  ANST (Analytical study); BIOL (Biological
       study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP
       (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or
       reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents:  ANST (Analytical
       study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP
       (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or
       reagent)

Absolute stereochemistry.
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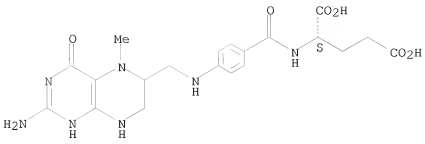

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1425 REFERENCES IN FILE CA (1907 TO DATE)
41 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1429 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> E "5-METHYLTETRAHYDROFOLIC ACID"/CN 25
E1 1 5-METHYLTETRAHYDROFOLATE:HOMOCYSTEINE S-METHYLTRANSFERASE (STREPTOMYCES CLAVULIGERUS STRAIN ATCC27064 GENE METH)/CN
E2 1 5-METHYLTETRAHYDROFOLATE:NAD OXIDOREDUCTASE/CN
E3 1 --> 5-METHYLTETRAHYDROFOLIC ACID/CN
E4 1 5-METHYLTETRAHYDROFOLIC ACID SODIUM SALT/CN
E5 1 5-METHYLTETRAHYDROFOLIC ACID-9,3',5'-3H/CN
E6 1 5-METHYLTETRAHYDROFURAN-2-ETHANOL/CN
E7 1 5-METHYLTETRAHYDROFURFURYL ALCOHOL/CN
E8 1 5-METHYLTETRAHYDROFUROIC ACID/CN
E9 1 5-METHYLTETRAHYDROHOMOFOLIC ACID/CN
E10 1 5-METHYLTETRAHYDROISOBENZOFURAN-1,3-DIONE/CN
E11 1 5-METHYLTETRAHYDROPHTHALIC ANHYDRIDE/CN
E12 1 5-METHYLTETRAHYDROPTERIN/CN
E13 1 5-METHYLTETRAHYDROPTEROYL HEPTAGLUTAMATE/CN
E14 1 5-METHYLTETRAHYDROPTEROYL HEXAGLUTAMATE/CN
E15 1 5-METHYLTETRAHYDROPTEROYL MONOGLUTAMATE/CN
E16 1 5-METHYLTETRAHYDROPTEROYL TETRAGLUTAMATE/CN
E17 1 5-METHYLTETRAHYDROPTEROYL TRIGLUTAMATE-HOMOCYSTEINE METHYLTRANSFERASE (SACCHAROMYCES CEREVISIAE STRAIN S288C GENE MET6)/CN
E18 1 5-METHYLTETRAHYDROPTEROYL-A-GLUTAMYLGLUTAMIC ACID/CN
E19 1 5-METHYLTETRAHYDROPTEROYL-Γ-GLUTAMYL-Γ-GLUTAMYLGLUTAMIC ACID/CN
E20 1 5-METHYLTETRAHYDROPTEROYL-Γ-HEPTAGLUTAMATE/CN
E21 1 5-METHYLTETRAHYDROPTEROYLDIGLUTAMIC ACID/CN
E22 1 5-METHYLTETRAHYDROPTEROYLGLUTAMIC ACID/CN
E23 1 5-METHYLTETRAHYDROPTEROYLPENTAGLUTAMATE/CN
E24 1 5-METHYLTETRAHYDROPTEROYLTRIGLUTAM ATE--HOMOCYSTEINE METHYLTRANSFERASE PROTEIN (RALSTONIA SOLANACEARUM STRAIN GMI1000 GENE METE)/CN
E25 1 5-METHYLTETRAHYDROPTEROYLTRIGLUTAMATE HOMOCYSTEINE METHYLTRANSFERASE/CN

=> E "5,10-METHYLENETETRAHYDROFOLIC ACID"/CN 25
E1 1 5,10-METHYLENETETRAHYDROFOLATE REDUCTASE RELATED PROTEIN (THERMOPLASMA ACIDOPHILUM STRAIN DSM1728 GENE TA0979)/CN
E2 1 5,10-METHYLENETETRAHYDROFOLATE REDUCTASE SEQUENCE HOMOLOG (KOCHIA SCOPARIA STRAIN LINE-254 C-TERMINAL FRAGMENT)/CN
E3 1 --> 5,10-METHYLENETETRAHYDROFOLIC ACID/CN
E4 1 5,10-METHYLENETETRAHYDROMETHANOPTERIN REDUCTASE (FRANKIA ALNI STRAIN ACN14A)/CN
E5 9 5,10-METHYLENETETRAHYDROMETHANOPTERIN REDUCTASE (RHODOCOCCUS STRAIN RHA1)/CN

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E6              1      5,10-METHYLENETETRAHYDROPTEROYLGLUTAMATE REDUCTASE/CN
E7              1      5,10-NITRILO-10A4-DIBENZO(B,E)(1,4)DITHIIN-5-IUM/CN
E8              1      5,10-NONACOSANEDIOL/CN
E9              1      5,10-NONACOSANEDIOL, 5,10-DIACETATE/CN
E10             1      5,10-NONACOSANEDIOL, DIACETATE/CN
E11             1      5,10-NONACOSANEDIONE/CN
E12             1      5,10-O-BENZENO-1,4-METHANOBENZO(B)BIPHENYLEN-17-ONE,
1,2,3,4-TETRACHLORO-1,4,4A,4B,5,10,10A,10B-OCTAHYDRO-5,10-DIMETHYL-, DIMETHYL
ACETAL/CN
E13             1      5,10-O-BENZENO-1,4-METHANOBENZO(B)BIPHENYLENE/CN
E14             1      5,10-O-BENZENO-1,4-METHANOBENZO(B)BIPHENYLENE,
1,2,3,4-TETRACHLORO-1,4,4A,4B,5,10,10A,10B-OCTAHYDRO-17,17-DIMETHOXY-5,10-DIMETHYL-+
/CN
E15             1      5,10-O-BENZENO-1,4-METHANOBENZO(B)BIPHENYLENE,
1,4,4A,4B,5,10,10A,10B-OCTAHYDRO-/CN
E16             1      5,10-O-BENZENO-10H-DIBENZO(A,D)CYCLOHEPTEN-10-OL,
5,11-DIHYDRO-/CN
E17             1      5,10-O-BENZENO-10H-DIBENZO(A,D)CYCLOHEPTEN-10-OL, 5,11-DIHYDRO-,
ACETATE/CN
E18             1      5,10-O-BENZENO-10H-DIBENZO(A,D)CYCLOHEPTENE/CN
E19             1      5,10-O-BENZENO-11H-BENZO(B)FLUOREN-11-ONE,
4B,5,10,10A-TETRAHYDRO-/CN
E20             1      5,10-O-BENZENO-11H-BENZO(B)FLUORENE/CN
E21             1      5,10-O-BENZENO-11H-DIBENZO(A,D)CYCLOHEPTEN-11-ONE,
5,10-DIHYDRO-/CN
E22             1      5,10-O-BENZENO-1H-PYRAZOLO(1,2-B)PHTHALAZINE/CN
E23             1      5,10-O-BENZENO-1H-PYRAZOLO(1,2-B)PHTHALAZINE-1,3(2H)-DIONE,
2,2-DIETHYL-5,10-DIHYDRO-/CN
E24             1      5,10-O-BENZENO-1H-S-TRIAZOLO(1,2-B)PHTHALAZINE/CN
E25             1      5,10-O-BENZENO-1H-S-TRIAZOLO(1,2-B)PHTHALAZINE-1,3(2H)-DIONE/CN

=> S E3
L25             1 "5,10-METHYLENETETRAHYDROFOLIC ACID"/CN

=> DIS L25 1 SQIDE

L25  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2010 ACS on STN
RN   3432-99-3  REGISTRY
CN   L-Glutamic acid, N-[4-(3-amino-1,2,5,6,6a,7-hexahydro-1-oxoimidazo[1,5-
     f]pteridin-8(9H)-yl)benzoyl]-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Glutamic acid, N-[p-(3-amino-5,6,6a,7-tetrahydro-1-hydroxyimidazo[1,5-
     f]pteridin-8(9H)-yl)benzoyl]-, L- (8CI)
CN   Imidazo[1,5-f]pteridine, L-glutamic acid deriv.
OTHER NAMES:
CN   (+)-5,10-Methylene-5,6,7,8-tetrahydrofolic acid
CN   5,10-Methylene-(6RS)-tetrahydrofolic acid
CN   5,10-Methylene-5,6,7,8-tetrahydrofolic acid
CN   5,10-Methylenetetrahydrofolic acid
CN   CoFactor
CN   Folic acid, tetrahydro-N5,N10-methylene-
CN   Folitixorin
CN   N5,N10-Methylene-5,6,7,8-tetrahydrofolic acid
CN   N5,N10-Methylenetetrahydrofolic acid
CN   N5,N10-Methylenetetrahydropteroylglutamic acid
FS   STEREOSEARCH
DR   14948-92-6, 23284-08-4, 39939-22-5, 42578-82-5
MF   C20 H23 N7 O6
CI   COM
LC   STN Files:   ADISINSIGHT, AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA,
       CAPLUS, CASREACT, CHEMCATS, CIN, DDFU, DRUGU, EMBASE, IMSDRUGNEWS,
       IMSPATENTS, IMSRESEARCH, MEDLINE, SYNTHLINE, TOXCENTER, USAN, USPAT2,
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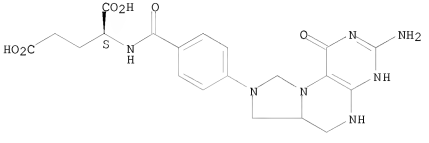
USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

590 REFERENCES IN FILE CA (1907 TO DATE)
62 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
590 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d his

(FILE 'HOME' ENTERED AT 13:07:18 ON 29 JAN 2010)

FILE 'REGISTRY' ENTERED AT 13:08:22 ON 29 JAN 2010
L1 3075 S TETRAHYDROFOLATE
L2 0 S TETRAHYDROFOLATE/CN
E "TETRAHYDROFOLATE"/CN 25
E "TETRAHYDROFOLIC ACID"/CN 25
L3 1 S E3
E "TETRAHYDROFOLIC ACID"/CN 25
E "METHYL-TETRAHYDROFOLATE"/CN 25
E "5-METHYLTETRAHYDROFOLATE"/CN 25
E "5-MTHF"/CN 25
E "5,10-METHYLENETETRA"/CN 25
E "5,10-METHYLENETETRAHYDROFOLATE"/CN 25
E "MTHF"/CN 25
L4 1 S E3

FILE 'CAPLUS' ENTERED AT 13:13:16 ON 29 JAN 2010
L5 1971 S L3 OR METHYLENE-TETRAHYDROFOLATE OR METHYL-TETRAHYDROFOLATE
L6 8 S L5 AND (PEMETREXED OR RALITREXED OR LOMETREXOL)
L7 8 DUP REM L6 (0 DUPLICATES REMOVED)

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     FILE 'REGISTRY' ENTERED AT 13:15:04 ON 29 JAN 2010
                E "METHYLENETETRAHYDROFOLATE"/CN 25
L8             8 S PEMETREXED
L9             0 S RALITREXED
L10            1 S RALTITREXED
L11            2 S LOMETREXOL

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:16:34 ON 29 JAN 2010

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L12          SEL L3 1- CHEM :      12 TERMS
                SET SMARTSELECT OFF

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L13         2719 S L12

     FILE 'REGISTRY' ENTERED AT 13:17:07 ON 29 JAN 2010
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L14          SEL L8 1- CHEM :      24 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:09 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
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L15          SEL L10 1- CHEM :       7 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:10 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
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L16          SEL L11 1- CHEM :       6 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:11 ON 29 JAN 2010
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L18         5017 S L15
L19          419 S L16
L20         8299 S L17 OR L18 OR L19
L21           69 S L13 AND L20
L22           66 S L21 AND PD<20041222
L23           47 DUP REM L22 (19 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 13:19:22 ON 29 JAN 2010

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:19:22 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:24:28 ON 29 JAN 2010
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L24            1 S E3
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                E "5,10-METHYLENETETRAHYDROFOLIC ACID"/CN 25
L25            1 S E3

=> d his

     (FILE 'HOME' ENTERED AT 13:07:18 ON 29 JAN 2010)

     FILE 'REGISTRY' ENTERED AT 13:08:22 ON 29 JAN 2010
L1          3075 S TETRAHYDROFOLATE
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L2            0 S TETRAHYDROFOLATE/CN
                E "TETRAHYDROFOLATE"/CN 25
                E "TETRAHYDROFOLIC ACID"/CN 25
L3            1 S E3
                E "TETRAHYDROFOLIC ACID"/CN 25
                E "METHYL-TETRAHYDROFOLATE"/CN 25
                E "5-METHYLTETRAHYDROFOLATE"/CN 25
                E "5-MTHF"/CN 25
                E "5,10-METHYLENETETRA"/CN 25
                E "5,10-METHYLENETETRAHYDROFOLATE"/CN 25
                E "MTHF"/CN 25
L4            1 S E3

     FILE 'CAPLUS' ENTERED AT 13:13:16 ON 29 JAN 2010
L5         1971 S L3 OR METHYLENE-TETRAHYDROFOLATE OR METHYL-TETRAHYDROFOLATE
L6            8 S L5 AND (PEMETREXED OR RALITREXED OR LOMETREXOL)
L7            8 DUP REM L6 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 13:15:04 ON 29 JAN 2010
                E "METHYLENETETRAHYDROFOLATE"/CN 25
L8            8 S PEMETREXED
L9            0 S RALITREXED
L10           1 S RALTITREXED
L11           2 S LOMETREXOL

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:16:34 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:16:40 ON 29 JAN 2010
                SET SMARTSELECT ON
L12          SEL L3 1- CHEM :      12 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:16:41 ON 29 JAN 2010
L13        2719 S L12

     FILE 'REGISTRY' ENTERED AT 13:17:07 ON 29 JAN 2010
                SET SMARTSELECT ON
L14          SEL L8 1- CHEM :      24 TERMS
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     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:09 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
                SET SMARTSELECT ON
L15          SEL L10 1- CHEM :       7 TERMS
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     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:10 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
                SET SMARTSELECT ON
L16          SEL L11 1- CHEM :       6 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:11 ON 29 JAN 2010
L17        3520 S L14
L18        5017 S L15
L19         419 S L16
L20        8299 S L17 OR L18 OR L19
L21          69 S L13 AND L20
L22          66 S L21 AND PD<20041222
L23          47 DUP REM L22 (19 DUPLICATES REMOVED)
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     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:19:22 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:24:28 ON 29 JAN 2010
                E "5-METHYLTETRAHYDROFOLIC ACID"/CN 25
L24           1 S E3
                E "5-METHYLTETRAHYDROFOLIC ACID"/CN 25
                E "5,10-METHYLENETETRAHYDROFOLIC ACID"/CN 25
L25           1 S E3

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    28.92     352.61

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -6.80

FILE 'CAPLUS' ENTERED AT 13:41:32 ON 29 JAN 2010
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FILE COVERS 1907 - 29 Jan 2010  VOL 152 ISS 6
FILE LAST UPDATED: 28 Jan 2010  (20100128/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Oct 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Oct 2009

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the third quarter of 2009.

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http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l3 or l24 or l25
          1253 L3
          1429 L24
           590 L25
L26       2619 L3 OR L24 OR L25

=> s l26 and (pemetrexed or raltitrexed or lometrexol)
           750 PEMETREXED
           585 RALTITREXED
           102 LOMETREXOL
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L27         19 L26 AND (PEMETREXED OR RALTITREXED OR LOMETREXOL)

=> dup rem l27
PROCESSING COMPLETED FOR L27
L28          19 DUP REM L27 (0 DUPLICATES REMOVED)

=> s l28 and ad<20041222
L29          19 S L28
       5146022 AD<20041222
                (AD<20041222)
L30           3 L29 AND AD<20041222

=> d l30 1-3 ibib abs

L30  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER:          2005:409543  CAPLUS
DOCUMENT NUMBER:           142:457053
TITLE:                     Human protein IAP (inhibitor of apoptosis protein)
                           nucleobase oligomers, including dsRNA, shRNA, and
                           siRNA, and their use for enhancing apoptosis in cancer
                           therapy
INVENTOR(S):               Lacasse, Eric; McManus, Daniel
PATENT ASSIGNEE(S):        Aegera Therapeutics, Inc., Can.
SOURCE:                    PCT Int. Appl., 112 pp.
                           CODEN: PIXXD2
DOCUMENT TYPE:             Patent
LANGUAGE:                  English
FAMILY ACC. NUM. COUNT:    1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
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     WO 2005042558        A1    20050512    WO 2004-CA1902           20041029 <--
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
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     US 20050148535       A1    20050707    US 2004-975974           20041028 <--
     CA 2542904           A1    20050512    CA 2004-2542904          20041029 <--
     EP 1682565           A1    20060726    EP 2004-789809           20041029 <--
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     JP 2007510408        T     20070426    JP 2006-537024           20041029 <--
PRIORITY APPLN. INFO.:                      US 2003-516192P      P   20031030
                                            WO 2004-CA1902       W   20041029

AB   The invention provides nucleobase oligomers and oligonucleotide duplexes
     that inhibit expression of an IAP (inhibitor of apoptosis protein), and
     methods for using them to induce apoptosis in a cell.  Specifically, the
     invention provides nucleic acid sequences for siRNAs and shRNAs that
     target human XIAP, HIAP-1 or HIAP-2 genes.  The nucleobase oligomers and
     oligomer complexes of the present invention may also be used to form
     pharmaceutical comps.  The invention also features methods for enhancing
     apoptosis in a cell by administering a nucleobase oligomer or oligomer
     complex of the invention in combination with a chemotherapeutic or
     chemosensitizing agent.  RNAi sequences and vectors producing shRNA (short
     hairpin RNA) were transfected into HeLa cells and evaluated for their
```

effect on XIAP, cIAP-1, or cIAP-2 protein levels. XIAP protein could also be reduced by RNAi clones in transfected breast cancer cell line MDA-MB-231. In addition, cell survival was reduced in XIAP RNAi transfected breast cancer cell line after the transfected cells were treated with TRAIL (tumor necrosis factor-related apoptosis inducing ligand).

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:409357 CAPLUS

DOCUMENT NUMBER: 142:457052

TITLE: Sequences of antisense IAP (inhibitor of apoptosis protein) oligomers and their use for treatment of proliferative diseases with a chemotherapeutic agent

INVENTOR(S): Lacasse, Eric; McManus, Daniel; Durkin, Jon P.

PATENT ASSIGNEE(S): Aegera Therapeutics, Inc., Can.

SOURCE: PCT Int. Appl., 285 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 2005042030	A1	20050512	WO 2004-CA1900	20041029	<--
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
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AU 2004284855	A1	20050512	AU 2004-284855	20041029	<--
CA 2542884	A1	20050512	CA 2004-2542884	20041029	<--
EP 1691842	A1	20060823	EP 2004-789807	20041029	<--
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CN 1901939	A	20070124	CN 2004-80039601	20041029	<--
JP 2007509861	T	20070419	JP 2006-537023	20041029	<--
ZA 2006003399	A	20070926	ZA 2006-3399	20041029	<--
NZ 547191	A	20090828	NZ 2004-547191	20041029	<--
RU 2376018	C2	20091220	RU 2006-117024	20041029	<--
SG 157422	A1	20091229	SG 2009-7918	20041029	<--
MX 2006004920	A	20070216	MX 2006-4920	20060502	
IN 2006MN00614	A	20070420	IN 2006-MN614	20060526	
NO 2006002420	A	20060731	NO 2006-2420	20060529	
KR 2006127393	A	20061212	KR 2006-710619	20060530	
PRIORITY APPLN. INFO.:			US 2003-516263P P	20031030	
			WO 2004-CA1900 W	20041029	

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention claims the use of an antisense oligomer to human XIAP, IAP-1 or IAP-2 genes and a chemotherapeutic agent, and compns. and kits thereof, for the treatment of proliferative diseases. The invention further claims

sequences for nucleobase oligomers that are antisense IAP (inhibitor of apoptosis protein) oligomers. The antisense IAP nucleobase oligomers specifically hybridize with polynucleotides encoding an IAP and reduce the amount of an IAP protein produced in a cell. Thus by reducing the IAP protein, the invention provides methods for inducing cancer cells to undergo apoptosis and for overriding anti-apoptotic signals in cancer cells. As an example of the invention, mice with s.c. H460 human lung carcinoma xenografts were injected intratumorally with XIAP antisense mixed-base 2'-O-Me RNA oligonucleotides (C5 and/or G4) and the drug vinorelbine. At the end of the 24 d treatment period, the mean relative tumor growth was reduced .apprx.70% in treated mice. The inhibition of tumor growth was correlated with down-regulation of human XIAP protein expression and an increased number of dead cells. The mice did not show any signs of cytotoxicity such as body weight loss.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:283298 CAPLUS

DOCUMENT NUMBER: 142:349042

TITLE: Combinations of chlorpromazine compounds and antiproliferative drugs for the treatment of neoplasms

INVENTOR(S): Lee, Margaret S.; Nichols, James M.; Zhang, Yanzhen; Keith, Curtis

PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA

SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005027842	A2	20050331	WO 2004-US30368	20040916 <--
WO 2005027842	A3	20051222		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004273910	A1	20050331	AU 2004-273910	20040916 <--
CA 2538570	A1	20050331	CA 2004-2538570	20040916 <--
EP 1670477	A2	20060621	EP 2004-788798	20040916 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004014568	A	20061107	BR 2004-14568	20040916 <--
CN 1878556	A	20061213	CN 2004-80033294	20040916 <--
JP 2007505914	T	20070315	JP 2006-527024	20040916 <--
MX 2006003066	A	20060620	MX 2006-3066	20060317
NO 2006001325	A	20060606	NO 2006-1325	20060323
KR 2007012618	A	20070126	KR 2006-707244	20060414
PRIORITY APPLN. INFO.:			US 2003-504310P P	20030918
			WO 2004-US30368 W	20040916

```
OTHER SOURCE(S):         MARPAT 142:349042
AB   The invention discloses a method for treating a patient having a cancer or
     other neoplasm by administering chlorpromazine or a chlorpromazine analog
     and an antiproliferative agent simultaneously or within 14 days of each
     other in amts. sufficient to treat the patient.
OS.CITING REF COUNT:     2     THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD
                               (3 CITINGS)


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     FILE 'REGISTRY' ENTERED AT 13:08:22 ON 29 JAN 2010
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                 E "5-MTHF"/CN 25
                 E "5,10-METHYLENETETRA"/CN 25
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L4             1 S E3

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L7             8 DUP REM L6 (0 DUPLICATES REMOVED)

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L18         5017 S L15
L19          419 S L16
L20         8299 S L17 OR L18 OR L19
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     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:19:22 ON 29 JAN 2010

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L30            3 S L28 AND AD<20041222

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L33  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER:         2005:409543  CAPLUS
DOCUMENT NUMBER:          142:457053
TITLE:                    Human protein IAP (inhibitor of apoptosis protein)
                          nucleobase oligomers, including dsRNA, shRNA, and
                          siRNA, and their use for enhancing apoptosis in cancer
                          therapy
INVENTOR(S):              Lacasse, Eric; McManus, Daniel
PATENT ASSIGNEE(S):       Aegera Therapeutics, Inc., Can.
SOURCE:                   PCT Int. Appl., 112 pp.
                          CODEN: PIXXD2
```

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005042558	A1	20050512	WO 2004-CA1902	20041029 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20050148535	A1	20050707	US 2004-975974	20041028 <--
CA 2542904	A1	20050512	CA 2004-2542904	20041029 <--
EP 1682565	A1	20060726	EP 2004-789809	20041029 <--
R: DE, FR, GB				
JP 2007510408	T	20070426	JP 2006-537024	20041029 <--

PRIORITY APPLN. INFO.: US 2003-516192P P 20031030
WO 2004-CA1902 W 20041029

AB The invention provides nucleobase oligomers and oligonucleotide duplexes that inhibit expression of an IAP (inhibitor of apoptosis protein), and methods for using them to induce apoptosis in a cell. Specifically, the invention provides nucleic acid sequences for siRNAs and shRNAs that target human XIAP, HIAP-1 or HIAP-2 genes. The nucleobase oligomers and oligomer complexes of the present invention may also be used to form pharmaceutical compns. The invention also features methods for enhancing apoptosis in a cell by administering a nucleobase oligomer or oligomer complex of the invention in combination with a chemotherapeutic or chemosensitizing agent. RNAi sequences and vectors producing shRNA (short hairpin RNA) were transfected into HeLa cells and evaluated for their effect on XIAP, cIAP-1, or cIAP-2 protein levels. XIAP protein could also be reduced by RNAi clones in transfected breast cancer cell line MDA-MB-231. In addition, cell survival was reduced in XIAP RNAi transfected breast cancer cell line after the transfected cells were treated with TRAIL (tumor necrosis factor-related apoptosis inducing ligand).

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2005:409357 CAPLUS
DOCUMENT NUMBER: 142:457052
TITLE: Sequences of antisense IAP (inhibitor of apoptosis protein) oligomers and their use for treatment of proliferative diseases with a chemotherapeutic agent
INVENTOR(S): Lacasse, Eric; McManus, Daniel; Durkin, Jon P.
PATENT ASSIGNEE(S): Aegera Therapeutics, Inc., Can.
SOURCE: PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005042030	A1	20050512	WO 2004-CA1900	20041029 <--
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AU 2004284855	A1	20050512	AU 2004-284855	20041029 <--
CA 2542884	A1	20050512	CA 2004-2542884	20041029 <--
EP 1691842	A1	20060823	EP 2004-789807	20041029 <--
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CN 1901939	A	20070124	CN 2004-80039601	20041029 <--
JP 2007509861	T	20070419	JP 2006-537023	20041029 <--
ZA 2006003399	A	20070926	ZA 2006-3399	20041029 <--
NZ 547191	A	20090828	NZ 2004-547191	20041029 <--
RU 2376018	C2	20091220	RU 2006-117024	20041029 <--
SG 157422	A1	20091229	SG 2009-7918	20041029 <--
MX 2006004920	A	20070216	MX 2006-4920	20060502
IN 2006MN00614	A	20070420	IN 2006-MN614	20060526
NO 2006002420	A	20060731	NO 2006-2420	20060529
KR 2006127393	A	20061212	KR 2006-710619	20060530
PRIORITY APPLN. INFO.:			US 2003-516263P P	20031030
			WO 2004-CA1900 W	20041029

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention claims the use of an antisense oligomer to human XIAP, IAP-1 or IAP-2 genes and a chemotherapeutic agent, and compns. and kits thereof, for the treatment of proliferative diseases. The invention further claims sequences for nucleobase oligomers that are antisense IAP (inhibitor of apoptosis protein) oligomers. The antisense IAP nucleobase oligomers specifically hybridize with polynucleotides encoding an IAP and reduce the amount of an IAP protein produced in a cell. Thus by reducing the IAP protein, the invention provides methods for inducing cancer cells to undergo apoptosis and for overriding anti-apoptotic signals in cancer cells. As an example of the invention, mice with s.c. H460 human lung carcinoma xenografts were injected intratumorally with XIAP antisense mixed-base 2'-O-Me RNA oligonucleotides (C5 and/or G4) and the drug vinorelbine. At the end of the 24 d treatment period, the mean relative tumor growth was reduced .apprx.70% in treated mice. The inhibition of tumor growth was correlated with down-regulation of human XIAP protein expression and an increased number of dead cells. The mice did not show any signs of cytotoxicity such as body weight loss.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:283298 CAPLUS

DOCUMENT NUMBER: 142:349042

TITLE: Combinations of chlorpromazine compounds and antiproliferative drugs for the treatment of neoplasms

INVENTOR(S): Lee, Margaret S.; Nichols, James M.; Zhang, Yanzhen;

Keith, Curtis
PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005027842	A2	20050331	WO 2004-US30368	20040916 <--
WO 2005027842	A3	20051222		
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004273910	A1	20050331	AU 2004-273910	20040916 <--
CA 2538570	A1	20050331	CA 2004-2538570	20040916 <--
EP 1670477	A2	20060621	EP 2004-788798	20040916 <--
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BR 2004014568	A	20061107	BR 2004-14568	20040916 <--
CN 1878556	A	20061213	CN 2004-80033294	20040916 <--
JP 2007505914	T	20070315	JP 2006-527024	20040916 <--
MX 2006003066	A	20060620	MX 2006-3066	20060317
NO 2006001325	A	20060606	NO 2006-1325	20060323
KR 2007012618	A	20070126	KR 2006-707244	20060414
PRIORITY APPLN. INFO.:			US 2003-504310P P	20030918
			WO 2004-US30368 W	20040916

OTHER SOURCE(S): MARPAT 142:349042
AB The invention discloses a method for treating a patient having a cancer or other neoplasm by administering chlorpromazine or a chlorpromazine analog and an antiproliferative agent simultaneously or within 14 days of each other in amts. sufficient to treat the patient.
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L33 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2001:78275 CAPLUS
DOCUMENT NUMBER: 134:141726
TITLE: Prodrug-based methods for treating therapy-resistant tumors, and prodrug screening method
INVENTOR(S): Shepard, H. Michael
PATENT ASSIGNEE(S): Newbiotics, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007088	A2	20010201	WO 2000-US20007	20000721 <--

WO 2001007088 A3 20011115
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
CA 2378187 A1 20010201 CA 2000-2378187 20000721 <--
AU 2000062318 A 20010213 AU 2000-62318 20000721 <--
AU 774492 B2 20040701
EP 1200130 A2 20020502 EP 2000-948885 20000721 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
BR 2000012676 A 20030701 BR 2000-12676 20000721 <--
JP 2003525866 T 20030902 JP 2001-511971 20000721 <--
MX 2002000762 A 20020820 MX 2002-762 20020121 <--
US 7419968 B1 20080902 US 2002-48033 20021127 <--
PRIORITY APPLN. INFO.: US 1999-145364P P 19990722
US 1999-153855P P 19990914
WO 2000-US20007 W 20000721

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 134:141726

AB A method is provided for selectively inhibiting a pathol. cell, in which the cell is characterized by expression of an endogenous, intracellular activating enzyme and in which the enzyme is not inactivated by a substrate prodrug compound The method requires contacting the cell with an effective amount of the substrate compound thereby selectively inhibiting the proliferation of the pathol. cell. The invention also provides a method for screening for prodrugs selectively converted to a toxin in a cell by an enzyme by contacting at least two test cells that express an endogenous, intracellular enzyme with the candidate prodrug from the same or different species and assaying for activation of the prodrug into toxic agents by the endogenous, intracellular enzyme. Compds. of the invention include uracil derivs. Preparation and testing of (E)-5-(2-bromovinyl)-2'-deoxy-5'-uridylphenyl-L-alaninylphosphoramidate is described.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2001:78274 CAPLUS
DOCUMENT NUMBER: 134:141719
TITLE: Enzyme-catalyzed anti-infective therapeutic agent prodrugs, preparation thereof, and screening method
INVENTOR(S): Shepard, H. Michael
PATENT ASSIGNEE(S): Newbiotics, Inc., USA
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007087	A2	20010201	WO 2000-US19844	20000721 <--
WO 2001007087	A3	20020117		

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            JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
            MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
            TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
            DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
            CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CA 2379834          A1    20010201    CA 2000-2379834          20000721 <--
     AU 2000063589       A     20010213    AU 2000-63589            20000721 <--
     EP 1202749          A2    20020508    EP 2000-950490           20000721 <--
        R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
           IE, SI, LT, LV, FI, RO, MK, CY, AL
     JP 2003527317       T     20030916    JP 2001-511970           20000721 <--
     MX 2002000761       A     20020812    MX 2002-761              20020121 <--
PRIORITY APPLN. INFO.:                      US 1999-145364P     P    19990722
                                            US 1999-153101P     P    19990909
                                            WO 2000-US19844     W    20000721

OTHER SOURCE(S):         MARPAT 134:141719
AB   A method is provided for selectively inhibiting an infectious agent or a
     cell infected by an infectious agent by contacting the infectious agent or
     the cell infected with the agent with a prodrug that is selectively
     converted to a toxin by an activating enzyme expressed by the infectious
     agent.  The activating enzyme is selective for the enzyme expressed by the
     infectious agent as compared to the same or similar enzyme expressed by
     the host cell or other infectious agents.  The activating agent is not
     inhibited nor inactivated by the prodrug.  Screens for identifying
     prodrugs are also provided herein.  Compds. of the invention include
     uracil derivs.  Preparation of e.g. (E)-5-(2-bromovinyl)-2'-deoxy-5'-
     uridylphenyl-L-alaninylphosphoramidate is described.
OS.CITING REF COUNT:     3      THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD
                                (3 CITINGS)
REFERENCE COUNT:         5      THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d his

     (FILE 'HOME' ENTERED AT 13:07:18 ON 29 JAN 2010)

     FILE 'REGISTRY' ENTERED AT 13:08:22 ON 29 JAN 2010
L1          3075 S TETRAHYDROFOLATE
L2             0 S TETRAHYDROFOLATE/CN
                 E "TETRAHYDROFOLATE"/CN 25
                 E "TETRAHYDROFOLIC ACID"/CN 25
L3             1 S E3
                 E "TETRAHYDROFOLIC ACID"/CN 25
                 E "METHYL-TETRAHYDROFOLATE"/CN 25
                 E "5-METHYLTETRAHYDROFOLATE"/CN 25
                 E "5-MTHF"/CN 25
                 E "5,10-METHYLENETETRA"/CN 25
                 E "5,10-METHYLENETETRAHYDROFOLATE"/CN 25
                 E "MTHF"/CN 25
L4             1 S E3

     FILE 'CAPLUS' ENTERED AT 13:13:16 ON 29 JAN 2010
L5          1971 S L3 OR METHYLENE-TETRAHYDROFOLATE OR METHYL-TETRAHYDROFOLATE
L6             8 S L5 AND (PEMETREXED OR RALITREXED OR LOMETREXOL)
L7             8 DUP REM L6 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 13:15:04 ON 29 JAN 2010
                 E "METHYLENETETRAHYDROFOLATE"/CN 25
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L8            8 S PEMETREXED
L9            0 S RALITREXED
L10           1 S RALTITREXED
L11           2 S LOMETREXOL

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     FILE 'REGISTRY' ENTERED AT 13:16:40 ON 29 JAN 2010
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L12          SEL L3 1- CHEM :      12 TERMS
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L13        2719 S L12

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L14          SEL L8 1- CHEM :      24 TERMS
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     FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
                SET SMARTSELECT ON
L15          SEL L10 1- CHEM :       7 TERMS
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     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:10 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:17:10 ON 29 JAN 2010
                SET SMARTSELECT ON
L16          SEL L11 1- CHEM :       6 TERMS
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     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:17:11 ON 29 JAN 2010
L17        3520 S L14
L18        5017 S L15
L19         419 S L16
L20        8299 S L17 OR L18 OR L19
L21          69 S L13 AND L20
L22          66 S L21 AND PD<20041222
L23          47 DUP REM L22 (19 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 13:19:22 ON 29 JAN 2010

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:19:22 ON 29 JAN 2010

     FILE 'REGISTRY' ENTERED AT 13:24:28 ON 29 JAN 2010
                E "5-METHYLTETRAHYDROFOLIC ACID"/CN 25
L24           1 S E3
                E "5-METHYLTETRAHYDROFOLIC ACID"/CN 25
                E "5,10-METHYLENETETRAHYDROFOLIC ACID"/CN 25
L25           1 S E3

     FILE 'CAPLUS' ENTERED AT 13:41:32 ON 29 JAN 2010
L26        2619 S L3 OR L24 OR L25
L27          19 S L26 AND (PEMETREXED OR RALTITREXED OR LOMETREXOL)
L28          19 DUP REM L27 (0 DUPLICATES REMOVED)
L29          19 S L28
L30           3 S L28 AND AD<20041222
L31          32 S L26 AND (L8 OR L10 OR L11)
L32           5 S L31 AND AD<20041222
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L33             5 DUP REM L32 (0 DUPLICATES REMOVED)

=>

---Logging off of STN---


=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      38.35     390.96

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                      -6.80     -13.60

STN INTERNATIONAL LOGOFF AT 13:44:09 ON 29 JAN 2010
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